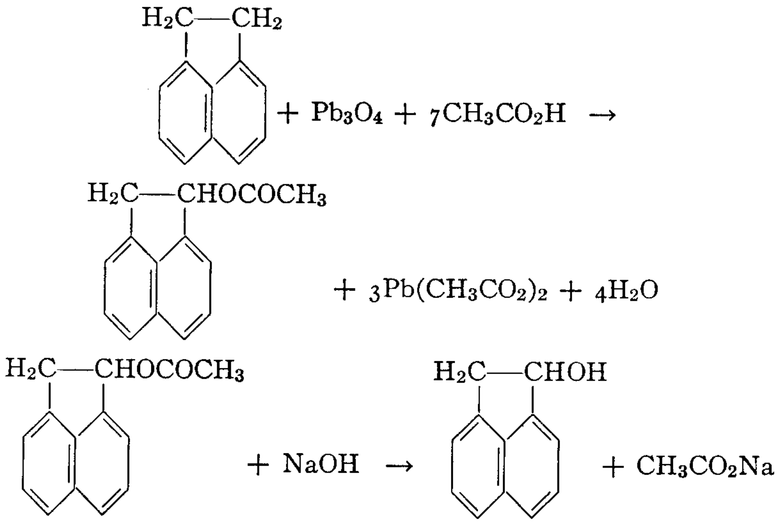
ACENAPHTHENOL-7



Submitted by JAMES CASON.
Checked by R. L. SHRINER and ELMER H. DOBRATZ.

1. Procedure

(*A*) *Acenaphthenol Acetate.*—In a 2-l. round-bottomed flask are placed 154 g. (1 mole) of acenaphthene (Note 1) and 1100 cc. of glacial acetic acid (Note 2). The flask is fitted with a tantalum or nichrome wire stirrer [1] and a thermometer extending below the surface of the liquid. The solution is stirred and heated to 60°, at which point the source of heat is removed and 820 g. of red lead (Note 3) is added in portions of about 50 g., each portion being added as soon as the color due to the previous portion has been discharged. During this operation, which requires thirty to forty minutes, the temperature is maintained at 60-70° (Note 4) by external cooling. The reaction is complete when a portion of the solution gives no test for lead tetraacetate (Note 5). The dark red syrupy solution (which may contain a few suspended particles of red lead and lead dioxide) is poured

[1] Hershberg, Ind. and Eng. Chem., Anal. Ed. **8**, 313 (1936). Org. Syn. **17**, 31.

into 2 l. of water contained in a 4-l. separatory funnel. The acetate is extracted with a 350-cc. portion of ether and then with a 250-cc. portion. The total extract is washed first with 100 cc. of water, then with 300 cc. of saturated sodium chloride solution and is finally dried over 50 g. of anhydrous sodium sulfate. The sodium sulfate is removed by filtration and washed colorless with three 50-cc. portions of dry ether. The combined filtrate and washings are placed in a 500-cc. Claisen flask with an inset side arm, and after distillation of the solvent, the acetate is distilled *in vacuo*. The acetate distils almost entirely at 166–168°/5 mm. (bath temperature 180–185°, raised to 220° at the end) as a mobile yellow oil. The yield is 170–175 g. (80–82 per cent of the theoretical amount) (Note 6).

(*B*) *Acenaphthenol.*—The acetate obtained as above is dissolved in 275 cc. of methanol in a 2-l. round-bottomed flask, and a solution of 40 g. (1.2 equiv.) of sodium hydroxide in 400 cc. of water is added (Note 7). This mixture is refluxed for two hours (Note 7) and then cooled below 20°. The yellow crystalline acenaphthenol is collected on a filter and washed well with about 1.5 l. of water. The crude product is air-dried (138–143 g.) and then dissolved in 2 l. of boiling benzene. The solution is treated with 6-8 g. of decolorizing carbon (Note 8) and filtered through a heated funnel. The orange-red filtrate is concentrated to about 1 l., and the acenaphthenol is allowed to crystallize. After filtering with suction and washing with cold benzene (about 500 cc.) until the wash solvent is colorless, the acenaphthenol is obtained as practically colorless needles, m.p. 144.5–145.5° (corr.) (Note 9). It weighs 117–121 g. From the filtrate may be obtained an additional quantity of material which on one recrystallization gives only 3–5 g. of pure acenaphthenol. The total yield amounts to 120–126 g. (70–74 per cent of the theoretical amount based on the acenaphthene).

2. Notes

1. The "95 per cent acenaphthene" sold by Reilly Tar and Chemical Corporation melts at 92.5–93.5° (corr.) and is quite satisfactory for use in this reaction. A recrystallized sample of

this acenaphthene (m.p. 93–93.5) or acenaphthene from the Gesellschaft für Teerverwertung (m.p. 93–93.5) gives no better yield of pure acenaphthenol.

2. The glacial acetic acid should be purified by distillation from potassium permanganate. About 30–50 g. of potassium permanganate for each 1.5 l. of acetic acid should be used.

3. Mallinckrodt's Analytical Reagent red lead (assay 85–90 per cent) was used. Merck's and Baker's N.F. V red lead are also quite satisfactory. Previously prepared lead tetraacetate is in no way preferable to red lead for this oxidation.

4. If the oxidation is carried out at 50° the yield is unaffected, but several hours are required to complete the addition. At 40°, the reaction is very slow and the yield is lowered.

5. A drop of the reaction mixture is placed on a moist piece of starch-iodide paper. The development of a blue color shows the presence of lead tetraacetate.

6. The acenaphthenol acetate contains small amounts of acenaphthene and acenaphthenone but is pure enough for the next step.

7. The dark violet color appearing on addition of the alkali is probably due to the presence of acenaphthenone. Crystalline acenaphthenol begins to separate almost immediately after the alkali has been added. Care must be taken in heating to refluxing because when heated too rapidly the acenaphthenol crystallizes suddenly from solution and the heat evolved may blow part of it out through the condenser.

8. If the charcoal treatment is omitted, the acenaphthenol obtained is light yellow but practically pure.

9. Marquis [2] reported the melting point as 148°; von Braun and Bayer [3] reported it as 146°.

3. Methods of Preparation

Acenaphthenol has been prepared in poor yield by the oxidation of acenaphthene with lead dioxide; [2] and it is among

[2] Marquis, Compt. rend. **182**, 1227 (1926).
[3] von Braun and Bayer, Ber. **59**, 920 (1926).

the products obtained by hydrogenation of acenaphthene quinone.[3] The above procedure is essentially that described more briefly in the literature.[4]

ACETOACETANILIDE

$$CH_3COCH{=}C{=}O + C_6H_5NH_2 \rightarrow CH_3COCH_2CONHC_6H_5$$

Submitted by JONATHAN W. WILLIAMS and JOHN A. KRYNITSKY.
Checked by NATHAN L. DRAKE and JOSEPH LANN.

1. Procedure

IN a 500-cc. round-bottomed, three-necked flask fitted with a reflux condenser, dropping funnel, and a mercury-sealed stirrer (Note 1) is placed a solution of 46 g. (0.5 mole) of dry aniline in 125 cc. of pure dry benzene. Stirring is started, and a solution of 42 g. (0.5 mole) of ketene dimer (p. 64) in 75 cc. of pure dry benzene is added dropwise over a period of half an hour. The reaction mixture is then heated under reflux on the steam bath for one hour. After the major portion of the benzene has been removed by distillation from the steam bath, the remainder is removed under reduced pressure. The residue is dissolved in 500 cc. of hot 50 per cent aqueous alcohol from which the acetoacetanilide separates on cooling. The mixture is cooled to 0° before filtration. A second crop of crystals can be obtained by adding 250 cc. of water to the mother liquor and cooling again (Note 2). The total yield of product, m.p. 82–83.5°, is 65 g. (74 per cent of the theoretical amount). Further purification by recrystallization from 300 cc. of 50 per cent alcohol yields 55 g. of a product which melts at 84–85°.

2. Notes

1. A simpler seal (p. 40, Note 1) of rubber tubing lubricated by glycerol is satisfactory.

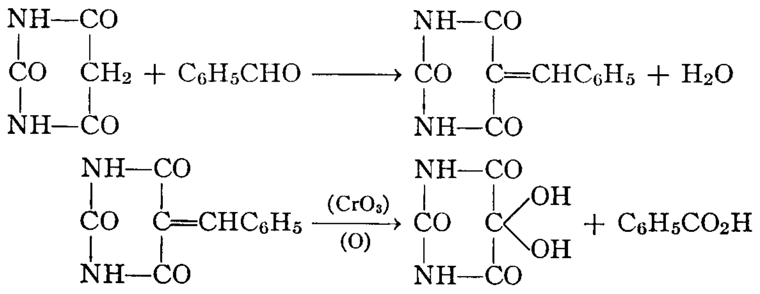
[4] Fieser and Cason, J. Am. Chem. Soc. **62**, 432 (1940).

2. If the second mother liquor is evaporated to about half of its original volume, a small third crop of very impure crystals may be obtained.

3. Methods of Preparation

Acetoacetanilide has been prepared by the reaction of aniline with ethyl acetoacetate[1,2,3] and by the reaction of ketene dimer with aniline.[4]

ALLOXAN MONOHYDRATE



Submitted by JOHN H. SPEER and THOMAS C. DABOVICH.
Checked by W. E. BACHMANN and R. O. EDGERTON.

1. Procedure

(*A*) *Benzalbarbituric Acid.*—A mixture of 128 g. (1 mole) of barbituric acid (Org. Syn. **18**, 8) and 1250 cc. of water in a 2-l. three-necked, round-bottomed flask equipped with an efficient stirrer and a reflux condenser is heated on a steam bath to effect solution (Note 1). When the acid has dissolved, 115 g. (110 cc., 1.08 moles) of benzaldehyde is added while heating and stirring are continued. The solution rapidly fills with the insoluble

[1] Knorr, Ann. **236**, 69 (1886).
[2] Roos, Ber. **21**, 624 (1888).
[3] Knorr and Reuter, ibid. **27** 1169 (1894).
[4] (*a*) Chick and Wilsmore, J. Chem. Soc. **1908**, 946; (*b*) Boese, Ind. Eng. Chem. **32**, 16 (1940).

benzalbarbituric acid. The mixture is heated for one hour on the steam bath to complete the reaction, and then filtered by suction (Note 2). The filter cake is washed with several portions of hot water and dried at 100°. The yield is 190–205 g. (88–95 per cent of the theoretical amount) of product possessing a very pale-yellow color. The substance melts at 254–256° and needs no further purification.

(*B*) *Alloxan Monohydrate.*—A mixture of 730 cc. of acetic acid, 95 cc. of water, and 162 g. (1.62 moles) of chromium trioxide (Note 3) is placed in a 2-l. three-necked, round-bottomed flask fitted with a stirrer and a thermometer, the stirrer is started, and the mixture is warmed to 50°. To the solution 180 g. (0.83 mole) of benzalbarbituric acid is added in small portions during the course of one-half hour, a cold water bath being used to maintain the temperature at 50–60°. After all the acid has been added, stirring is continued and the temperature maintained at 50–60° by a warm water bath for another half-hour to complete the reaction. Alloxan monohydrate generally starts to crystallize from the warm solution. The mixture is cooled to 15° and filtered. The product is washed on the filter with cold glacial acetic acid until the washings are no longer green, and then dried by washing with ether. The yield is 105–112 g. (79–84 per cent of the theoretical amount) of yellow crystals which melt at about 254° (Note 4) with decomposition and are sufficiently pure for most purposes.

In order to obtain practically colorless alloxan monohydrate (Note 5), 25 g. of the yellow crystals is dissolved in 37 cc. of hot water, the solution is boiled with Norite, and the hot solution is filtered into a 500-cc. round-bottomed flask. About 15–20 cc. of water is removed by distillation under reduced pressure on a water bath. The colorless crystalline residue is dissolved in the minimal volume of hot water, the solution is cooled somewhat, and to it is added 250 cc. of glacial acetic acid. After the mixture has been kept cold (5–10°) for four to six hours, the alloxan monohydrate is filtered. The yield is 20–21 g. (80–84 per cent recovery) (Note 6) of practically colorless crystals which melt at about 254° (Note 7) with decomposition.

2. Notes

1. The submitters report that a single attempt to use the aqueous-alcoholic solution of barbituric acid obtained in Org. Syn. **18**, 8, before recrystallization of the product gave an excellent yield of an apparently isomeric product unsuited for the preparation of alloxan.

2. This filtration may be done hot or cold at the convenience of the operator.

3. The technical grade (flakes) was found quite satisfactory.

4. This value is obtained in a Pyrex capillary tube; the solid remains yellow until about 254° when it suddenly decomposes to a red melt with vigorous evolution of gas. When a soft-glass capillary tube is used, the solid assumes a red color at about 180–200° and melts between 240° and 250°.

5. By recrystallization of the yellow product from glacial acetic acid (12 cc. per g.), using Norite, the checkers invariably obtained yellow crystals (75–80 per cent recovery) instead of the practically colorless crystals reported by the submitters. By adding a volume of water equal to the weight of crystals to the hot acetic acid solution, the checkers obtained a pale-yellow product.

6. This represents the first crop of crystals.

7. This value is obtained in a Pyrex capillary tube. The colorless solid begins to turn yellow at about 180° and melts at about 254° (occasionally 258–260°) to a red liquid with vigorous evolution of gas.

3. Methods of Preparation

Alloxan monohydrate has been prepared by the oxidation of uric acid with chlorine,[1,2] or potassium chlorate and hydrochloric acid;[3] by the oxidation of alloxantin,[4] xanthine,[5] uramil,[4] and

[1] McElvain, J. Am. Chem. Soc. **57**, 1303 (1935).
[2] Biltz and Heyn, Ann. **413**, 60 (1917).
[3] Fischer and Helferich, "Anleitung zur Darstellung organischer Präparate," 10th Ed., p. 66, Braunschweig, 1922.
[4] Wöhler and Liebig, Ann. **26**, 256 (1838).
[5] Fischer, ibid. **215**, 310 (1882).

thiouramil;[6] and by the hydrolysis of dibromobarbituric acid.[7] The method here described is originally due to Biilmann and Berg.[8]

ALUMINUM *tert.*-BUTOXIDE

$$3(CH_3)_3COH + Al \rightarrow Al[OC(CH_3)_3]_3 + 3(H)$$

Submitted by WINSTON WAYNE and HOMER ADKINS.
Checked by NATHAN L. DRAKE, WM. H. SOUDER, JR., and RALPH MOZINGO.

1. Procedure

IN a 2-l. round-bottomed flask, bearing a reflux condenser protected by a calcium chloride tube, are placed 64 g. (2.37 gram atoms) of aluminum shavings, 200 g. (254 cc., 2.7 moles) of dry *tert.*-butyl alcohol, and 5 to 10 g. of aluminum *tert.*-butoxide (Note 1). After the mixture is heated to boiling on a steam bath, approximately 0.4 g. of mercuric chloride is added followed by vigorous shaking (Note 2). As the heating is continued the color of the reaction mixture gradually changes from clear to milky to black, and hydrogen is evolved. When the mixture has become black, the heating is interrupted.

After the reaction has been allowed to proceed for an hour without heating, an additional 244 g. (309 cc., 3.3 moles) of dry *tert.*-butyl alcohol (total quantity, 6 moles) and 200 cc. of dry benzene are added. The reaction will again set in upon gentle heating and will continue vigorously without further heating. After about two hours the reaction subsides and the mixture is refluxed for about ten hours.

The benzene and unchanged *tert.*-butyl alcohol are removed by distillation from the steam bath, the final traces being removed under 10–30 mm. pressure. A liter of *dry* ether is added, and the solid aluminum *tert.*-butoxide is dissolved by refluxing for a short

[6] Fischer and Ach, Ann. **288**, 160 (1895).
[7] Baeyer, ibid. **127**, 230 (1863); **130**, 131 (1864).
[8] Biilmann and Berg, Ber. **63B**, 2201 (1930).

period. After cooling, 35 cc. of *undried* ether is added, followed immediately by vigorous shaking (Note 3). After standing for two hours the solution is centrifuged for thirty minutes to remove unused aluminum, aluminum hydroxide, and mercury (Note 4).

The solvent is removed by distillation from the steam bath, the final traces under 10–30 mm. pressure. The flask is allowed to cool with a calcium chloride tube attached, and the product crushed with a spatula and transferred to bottles sealed against moisture. The yield is 394–418 g. (80–85 per cent of the theoretical amount) of a white or slightly gray solid.

2. Notes

1. Commercial *tert.*-butyl alcohol dried over calcium oxide is suitable for this preparation. Aluminum isopropoxide or ethoxide [1, 2] may be used in place of the aluminum *tert.*-butoxide to remove traces of water. The grade of metal known as "fast cutting rods" has proved most satisfactory. The checkers used turnings made from aluminum cast from melted-down kitchen utensils. Aluminum *tert.*-butoxide has also been prepared successfully in another laboratory from commercially pure aluminum (2S) and from rods of the alloy 17ST (communication from L. F. Fieser). The checkers were able to obtain considerably higher yields of the butoxide from pure aluminum than from a copper-bearing alloy.

2. The use of larger amounts of mercuric chloride increases the difficulty of getting the final product free from color. This difficulty may be avoided by previously amalgamating the aluminum.[3, 4] The mixture is shaken to distribute the mercuric chloride and thus aid in an even amalgamation of the aluminum.

3. The small amount of water introduced with the undried ether forms aluminum hydroxide which aids in the precipitation

[1] Tischtschenko, J. Russ. Phys. Chem. Soc. **31**, 694 (1899) [Chem. Zentr. **71**, I, 10 (1900)].
[2] Young, Hartung, and Crossley, J. Am. Chem. Soc. **58**, 100 (1936).
[3] Wislicenus and Kaufman, Ber. **28**, 1325 (1895).
[4] Adkins, J. Am. Chem. Soc. **44**, 2175 (1922).

of the black suspended material. Shaking is essential to obtain the hydroxide formation throughout the solution.

4. The centrifuging may be carried out in 250-cc. stoppered bottles at 2000 r.p.m. After centrifuging, the solution should be colorless or light tan. If it is still dark in color another 25-cc. portion of undried ether should be added and the centrifuging repeated.

3. Methods of Preparation

Aluminum *tert.*-butoxide can be prepared by refluxing dry *tert.*-butyl alcohol with amalgamated aluminum [1, 5, 6] or aluminum plus mercuric chloride.[6] The method described is that of Adkins and Cox.[6] The preparation of amalgamated aluminum has been described.[3, 4] Aluminum isopropoxide can be prepared from dry isopropyl alcohol and aluminum,[1, 2] the method being essentially that described for aluminum ethoxide (Org. Syn. **15**, 82).

o-AMINOBENZYL ALCOHOL

$$o\text{-}NH_2C_6H_4CO_2H + 4H \rightarrow o\text{-}NH_2C_6H_4CH_2OH + H_2O$$

Submitted by George H. Coleman and Herbert L. Johnson.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

The reduction is carried out in four cells of the type shown in Fig. 1. Each cell consists of a 1-l. beaker (B), a porous cup (P), a mechanical stirrer, and sheet lead electrodes (E_1 and E_2) each having a total surface area of 100 sq. cm. (Note 1). In the cathode space of each cell are placed 25 g. (0.18 mole) of anthranilic acid (Note 2) and 400 cc. of 15 per cent sulfuric acid. In each porous cup is placed 200 cc. of 15 per cent sulfuric acid. The cells are connected in series as shown in Fig. 1 with an ammeter (A) and suitable resistance (R) (Note 3) also in the circuit.

[5] Oppenauer, Rec. trav. chim. **56**, 137 (1937).
[6] Adkins and Cox, J. Am. Chem. Soc. **60**, 1151 (1938).

The stirrers are started, the current (110 volt D.C.) turned on, and the resistance so adjusted that the ammeter records 10–12 amperes. The temperature of the solution in the cells is maintained at 20–30° by surrounding them with a bath of cool water (Note 4). The reduction is complete after 60–70 ampere-hours. This fact is indicated by the increased evolution of hydrogen and the complete solution of the anthranilic acid.

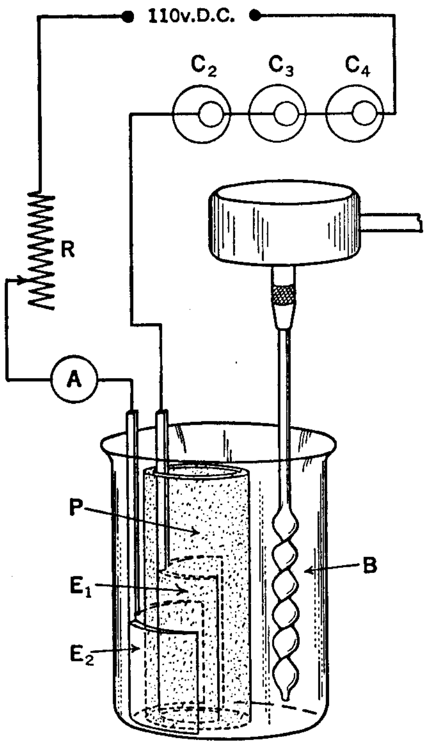


Fig. 1

The cathode liquid is removed from the cells and neutralized with solid ammonium carbonate or concentrated aqueous ammonia. The solution is filtered to remove any resinous material, then saturated with ammonium sulfate and extracted with five 80-cc. portions of chloroform (Note 5). The chloroform solution is dried with 20 g. of anhydrous sodium or magnesium sulfate, filtered, and the chloroform removed by evaporation on a steam bath (Note 6). The yield of *o*-aminobenzyl alcohol obtained from the four cells is 62–70 g. (69–78 per cent of the theoretical amount).

This product has a light brown color and melts at 75–80°. After one recrystallization from petroleum ether the melting point is 80–81° (Note 7).

2. Notes

1. Ordinary sheet lead of 99.9 per cent purity is satisfactory.
2. The anthranilic acid melted at 143–144°.

3. A resistance of 10–12 ohms is required for the apparatus described. It may be necessary to adjust the rheostat several times during the course of the reaction.

4. The checkers found it necessary to cool the cells by frequent addition of ice to the water bath surrounding them.

5. Ethyl ether may be used in place of chloroform but is not so satisfactory since several more extractions are necessary to remove the same amount of product from the aqueous solution.

6. The evaporation may be carried out in an apparatus which permits recovery of the solvent.

7. Petroleum ether boiling at 65–75° is used for recrystallization. The product has a limited solubility even in the hot solvent, and a relatively large volume is therefore required.

3. Methods of Preparation

o-Aminobenzyl alcohol has been prepared by the reduction of *o*-nitrobenzaldehyde [1, 2] or *o*-nitrobenzyl alcohol [3, 4] with zinc and hydrochloric acid in alcoholic solution. The present method of preparing *o*-aminobenzyl alcohol is a modification of that described by Mettler.[5] Other substituted benzyl alcohols have been prepared by the same method.

[1] Friedlander and Henriques, Ber. **15**, 2109 (1882).
[2] Paal and Senniger, ibid. **27**, 1084 (1894).
[3] Gabriel and Posner, ibid. **27**, 3512 (1894).
[4] Auwers, ibid. **37**, 2260 (1904).
[5] Mettler, ibid. **38**, 1751 (1905).

n-CAPROIC ANHYDRIDE

$$2CH_3(CH_2)_4CO_2H + CH_2{=}C{=}O \rightarrow [CH_3(CH_2)_4CO]_2O + CH_3CO_2H$$

Submitted by JONATHAN W. WILLIAMS and JOHN A. KRYNITSKY.
Checked by NATHAN L. DRAKE and JOSEPH LANN.

1. Procedure

ONE HUNDRED AND SIXTEEN grams (126 cc., 1 mole) of *n*-caproic acid is placed in a 250-cc. gas-washing bottle. The bottle is supported in an ice bath, and 0.50 to 0.55 mole of ketene is passed into the acid at a rate of approximately 0.45 mole per hour (Notes 1 and 2).

The resulting mixture is transferred to an apparatus for fractional distillation, and carefully fractionated, an oil bath being used for heating (Note 3). A low-boiling fraction, consisting of acetone containing some ketene, acetic acid, and a small quantity of acetic anhydride, is removed at atmospheric pressure. As the distillation progresses the temperature of the oil bath is raised to 220° over a period of about an hour and held there until three hours have elapsed from the time distillation started (Note 4).

The distillation at atmospheric pressure is then discontinued, the liquid is allowed to cool somewhat, and distillation is continued at a pressure of 3–10 mm. After a fore-run of less than 20 g., *n*-caproic anhydride is collected (b.p. 109–112°/3 mm., 118–121°/6 mm.). The yield is 86–95 g. (80–87 per cent of the theoretical amount) (Note 5).

2. Notes

1. Ketene may be generated conveniently, at the proper rate, in the apparatus described by Williams and Hurd.[1]

2. Addition of one mole of ketene per mole of acid does not increase the yield. Under these conditions more acetic anhydride is found in the low-boiling fraction.

[1] Williams and Hurd, J. Org. Chem. **5**, 122 (1940).

3. Submitters and checkers used a column of the Whitmore-Lux type,[2] 12 mm. in diameter, 50 cm. long, packed with glass helices (Org. Syn. **20,** 96, Note 8), and provided with the usual jackets for heating. A less efficient column will serve in the preparation of caproic anhydride but not in the preparation of propionic anhydride or butyric anhydride by the same method.

4. It is imperative to continue the distillation at atmospheric pressure until conversion of any mixed anhydride to caproic anhydride is complete. The acetic acid formed by this conversion comes off very slowly, and approximately three hours are necessary to complete the distillation at atmospheric pressure.

5. According to the submitters, equally good yields can be obtained in the preparation of propionic anhydride and *n*-butyric anhydride.

3. Methods of Preparation

n-Caproic anhydride has been prepared by heating caproic acid with acetic anhydride,[3] by heating sodium caproate and acetic anhydride in a sealed tube,[4] by the action of phosphorus oxychloride on barium caproate,[5] by the action of acetyl chloride on caproic acid,[6] and by treating a mixture of sodium caproate and sulfur with chlorine.[7] The method used in the present synthesis was first described by Hurd and Dull.[8]

[2] Whitmore and Lux, J. Am. Chem. Soc. **54**, 3451 (1932).
[3] Autenrieth, Ber. **34**, 168 (1901).
[4] Michael, ibid. **34**, 918 (1901).
[5] Chiozza, Ann. **86**, 359 (1853).
[6] Fournier, Bull. soc. chim. (4), **5**, 920 (1909).
[7] Brit. pat. 24,842 (1908) [C. A. **4**, 2190, 2719 (1910)].
[8] Hurd and Dull, J. Am. Chem. Soc. **54**, 3427 (1932).

CATALYST, RANEY NICKEL

$$NiAl_2 + 6NaOH \rightarrow Ni + 2Na_3AlO_3 + 3H_2$$

Submitted by Ralph Mozingo.
Checked by Homer Adkins and Lawrence Richards.

1. Procedure

A solution of 380 g. of sodium hydroxide in 1500 cc. of distilled water, contained in a 4-l. beaker (Note 1) equipped with an efficient stirrer (Note 2), is cooled in an ice bath to 10°, and 300 g. of nickel-aluminum alloy (Note 3) is added to the solution in small portions, with stirring, at such a rate that the temperature does not rise above 25° (Note 4), the beaker being allowed to remain in the ice bath. When all the alloy has been added (about two hours is required) the stirrer is stopped, the beaker is removed from the ice bath, and the contents are allowed to come to room temperature. After the evolution of hydrogen becomes slow, the reaction mixture is allowed to stand on a steam bath until the evolution of hydrogen again becomes slow (about eight to twelve hours). The heating should not be too rapid at the beginning or the solution may foam over. During this time the volume of the solution is maintained constant by adding distilled water if necessary. After heating, the nickel is allowed to settle and most of the liquid is decanted. Distilled water is then added to bring the solution to the original volume; the nickel is suspended by stirring, again allowed to settle, and the solution is decanted. The nickel is then transferred to a 2-l. beaker (Note 5) with the aid of distilled water, and the water is again decanted. A solution of 50 g. of sodium hydroxide in 500 cc. of distilled water is added; the catalyst is suspended and allowed to settle; and the alkali is decanted. The nickel is washed by suspension in distilled water and decantation until the washings are neutral to litmus and then ten times more to remove the alkali completely (twenty to forty washings are required) (Note 6). The washing process is repeated three times

with 200 cc. of 95 per cent alcohol and three times with absolute alcohol; the catalyst is then stored under absolute alcohol in bottles which are completely filled with absolute alcohol and tightly closed (Note 7). The product is highly pyrophoric and must be kept under a liquid at all times. The Raney nickel contained in the suspension weighs about 150 g. (Note 8).

To prepare the catalyst under methylcyclohexane (Note 9), the catalyst, which has been prepared as above and washed free of alkali with water, but to which no alcohol has been added, is covered with 1 l. of methylcyclohexane which is distilled from an oil bath until all the water has been codistilled with the hydrocarbon, more of the methylcyclohexane being added from time to time so that the nickel always remains covered. When the catalyst is free from water it becomes freely suspended in the liquid.

To prepare nickel under dioxane, dioxane (Note 10) is used in place of the methylcyclohexane above and the distillation is continued until the temperature of the vapor reaches 101°. (*Caution. Do not use nickel in dioxane above 210°; the dioxane may react almost explosively with hydrogen and Raney nickel above this temperature.*)

2. Notes

1. A Pyrex battery jar of about 10-l. capacity is also suitable and is sufficiently large for the preparation of a batch of catalyst of two to three times the size given here.

2. The stirrer should be provided with a motor which will not ignite the hydrogen. Either an induction motor or an air stirrer may be used. The stirrer blades may be made of glass, Monel, or stainless steel.

3. The alloy used is " Raney Nickel Aluminum Catalyst Powder " from the Gilman Paint and Varnish Company, Chattanooga, Tenn. It contains about 50 per cent nickel.

4. The thermometer should not be left in the alkali or the bulb may be eaten away. The catalyst is inactivated by mercury. If the mixture foams badly at this point, 2 cc. of *n*-octyl alcohol may be added to prevent excessive foaming; however, this is not usually necessary.

5. A stoppered graduate of 2-l. capacity is somewhat more convenient than a 2-l. beaker.

6. The number of washings required may be materially reduced by allowing time for diffusion of base from the surface of the catalyst into the surrounding wash water. To this end the catalyst is stirred well with 1.5 l. of water for each washing. Diffusion is allowed to proceed for three to ten minutes, and the mixture is then stirred again and the wash water decanted as soon as the catalyst settles to the bottom. By this method twenty washings should be sufficient to remove all traces of the alkali adsorbed on the catalyst surface.

7. The quantity of catalyst prepared should not be larger than necessary for a six months' supply as the catalyst may deteriorate on standing.

8. It is more convenient to measure the catalyst than to weigh it. Raney nickel in alcohol contains about 0.6 g. of the catalyst per cubic centimeter of the settled material. The half and quarter teaspoons used in kitchens are convenient for measuring the catalyst. A level teaspoonful is about 3 g. of nickel.

9. It is necessary that the catalyst be freely suspended in the reaction mixture during a reduction. Therefore, the liquid under which the nickel is placed must be soluble in the reduction mixture at all times, i.e., in both the reactants and products.

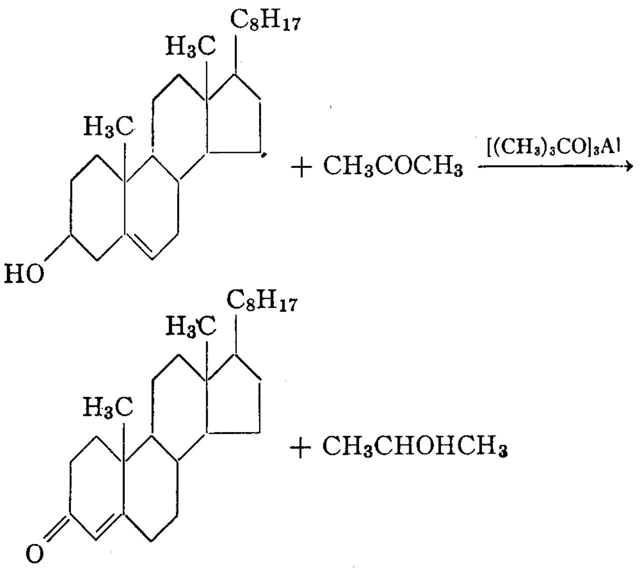
10. The dioxane used should be dry, halogen-free, and distilled from sodium.

3. Methods of Preparation

Raney nickel catalyst has been prepared from the nickel-aluminum alloy [1] by the action of sodium hydroxide solution.[2]

[1] Murray Raney, U. S. pat. 1,628,190 (1927).
[2] Covert and Adkins, J. Am. Chem. Soc. **54**, 4116 (1932).

CHOLESTENONE



Submitted by R. V. Oppenauer.
Checked by J. Cason and L. F. Fieser.

1. Procedure

A carefully dried 5-l. round-bottomed flask equipped with a reflux condenser carrying a calcium chloride tube is charged with 100 g. of cholesterol (Note 1), 750 cc. of acetone (Note 2), and 1000 cc. of benzene (Note 3). A boiling tube is introduced to prevent bumping (Note 4), and the mixture is heated to boiling in an oil bath which is maintained at 75–85° during the reaction. A solution of 80 g. of aluminum *tert.*-butoxide (p. 8) in 500 cc. of dry benzene is added in one portion to the boiling solution. The mixture turns cloudy and in ten to fifteen minutes develops a yellow color. Gentle boiling is continued at a bath temperature of 75–85° for a total of eight hours. The mixture is then cooled, treated with 200 cc. of water and then 500 cc. of 10 per cent sulfuric acid, shaken vigorously, and transferred to a 5-l. separatory funnel. The mixture is diluted with 1.5 l. of water and shaken for several minutes, after which the yellow aqueous layer is drawn off into a second separatory funnel and shaken out with a small amount of benzene (Note 5). The combined benzene extracts are washed thoroughly with water and dried by filtration through a layer of sodium sulfate; the solvent is evaporated, the last traces being removed by heating the residue at 60° at the water pump vacuum. The oily yellow residue solidifies when it is cooled in an ice-salt bath and scratched. For crystallization the material is dissolved in a mixture of 70 cc. of acetone and 100 cc. of methanol; the solution is allowed to cool very slowly and is seeded, for otherwise the product tends to separate as an oil. After the bulk of the material has crystallized, the mixture is allowed to stand for one day at 0°; the product is then collected, washed with 100 cc. of ice-cold methanol, and dried in vacuum at room temperature. The yield of almost colorless cholestenone, m.p. 77–79°, is 70–81 g. (70–81 per cent of the theoretical amount). Recrystallization by the same method gives material melting at 78.5–80.5° with 90 per cent recovery (Notes 6 and 7).

2. Notes

1. The material should be dried to constant weight at 80–100° in vacuum. Commercial cholesterol, m.p. 146–148.5°, gives satisfactory results; the yield is raised 5–10 per cent by using cholesterol which has been purified by regeneration from the dibromide.

2. The acetone is distilled once from permanganate and twice from freshly fused potassium hydroxide.

3. The benzene is distilled over sodium.

4. If boiling stones are employed, fresh ones must be added at intervals; the boiling tube promotes smooth boiling at the bath temperature specified.

5. The troublesome emulsions sometimes encountered are easily broken by filtration from a trace of suspended solid.

6. For recovery of material in the mother liquors, the solutions are subjected to steam distillation to remove solvents and

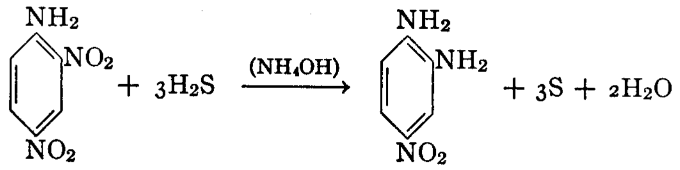
condensation products from the acetone. The process is continued until the distillate is odorless (one to two hours), and the residual oil is dried by heating it in vacuum on the steam bath. From a solution in acetone-methanol (20 and 50 cc., respectively) there is obtained after some manipulation (slow cooling, scratching) 3.3 g. of crude cholestenone, m.p. 72–80° (cloudy melt).

7. The yield is reduced by about 5 per cent by halving the amounts of acetone and benzene specified and using only 50 g. of aluminum *tert.*-butoxide.

3. Methods of Preparation

Cholestenone has been prepared by oxidation of cholesterol dibromide with chromic acid [1] or potassium permanganate [2] and debromination, and by dehydrogenation of cholesterol over copper oxide [3, 4] or by the method described above.[5]

1,2-DIAMINO-4-NITROBENZENE



Submitted by K. P. Griffin and W. D. Peterson.
Checked by Nathan L. Drake, Ralph Mozingo, and Jonathan Williams.

1. Procedure

A 5-l. three-necked flask is fitted with a mechanical stirrer, a reflux condenser, a thermometer, and an inlet tube extending to the bottom of the flask (Note 1). In the flask is placed a mixture of 238 g. (1.3 moles) of 2,4-dinitroaniline (Org. Syn. **15**, 22), 2400 cc. of 95 per cent ethyl alcohol, and 1200 cc. of concentrated ammonium hydroxide (sp. gr. 0.90).

[1] Windaus, Ber. **39**, 518 (1906).
[2] Schoenheimer, J. Biol. Chem. **110**, 461 (1935).
[3] Diels and Abderhalden, Ber. **37**, 3099 (1904).
[4] Diels, Gädke, and Körding, Ann. **459**, 21 (1927).
[5] Oppenauer, Rec. trav. chim. **56**, 137 (1937).

The mixture is heated to 45°, and with good stirring hydrogen sulfide is passed into the reaction mixture while its temperature is maintained between 45° and 55° (Notes 2 and 3). The yellow suspended particles of 2,4-dinitroaniline dissolve slowly to form an intensely red-colored solution. The reaction is complete when all the *yellow* particles have disappeared; reduction should be complete in thirty to sixty minutes (Note 4).

The reaction mixture is allowed to stand in an icebox for sixteen to eighteen hours to complete the separation of the product, which forms small, well-defined, deeply red-colored crystals. The 1,2-diamino-4-nitrobenzene is filtered by suction, washed with 150–250 cc. of cold water, and sucked dry on the funnel (Note 5).

The crude product is purified by dissolving it in a boiling mixture of 900 cc. of water and 110 cc. of concentrated hydrochloric acid (sp. gr. 1.19), and filtering the hot solution through a Norite bed using suction. The filter bed is washed with a boiling mixture of 90 cc. of water and 10 cc. of concentrated hydrochloric acid, and the washings are added to the main body of the solution. The filtered solution, while still hot, is treated with 100 cc. of concentrated ammonia (sp. gr. 0.90). The precipitated 1,2-diamino-4-nitrobenzene is filtered hot on a Büchner funnel, washed on the funnel with 150 cc. of water, and dried in an oven at 40–50°.

The purified material melts at 197–198° and weighs 105–115 g. (52–58 per cent of the theoretical amount).

2. Notes

1. The inlet tube should have a diameter of about 15 mm.

2. Enough heat is generated so that it is necessary to play a stream of cold water on the flask from time to time to maintain this temperature.

3. The rate of the gas stream should be as rapid as is consistent with complete absorption.

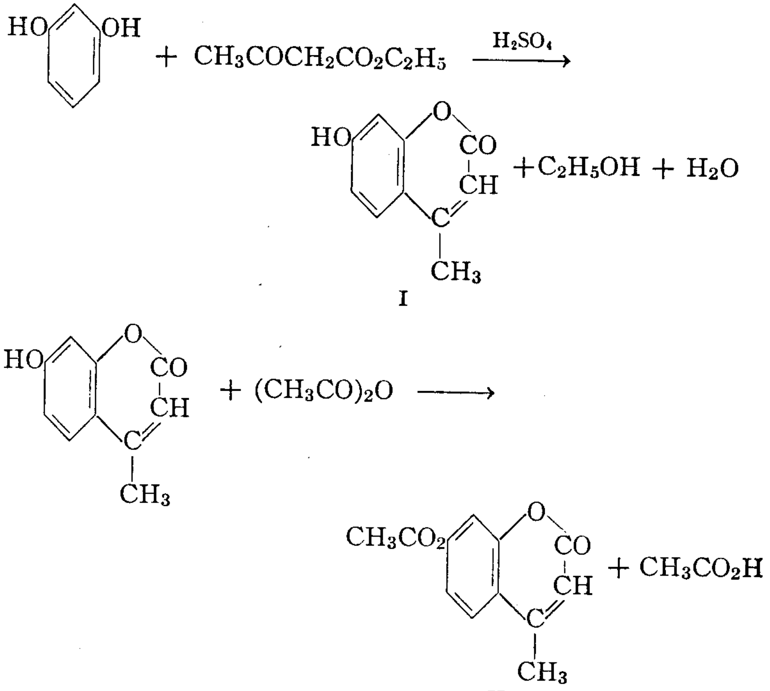
4. The product may begin to separate during the last few minutes.

5. Concentration of the mother liquor yields only a few grams of material (8–10 g.), a mixture of 1,4-diamino-2-nitrobenzene and 1,2-diamino-4-nitrobenzene.

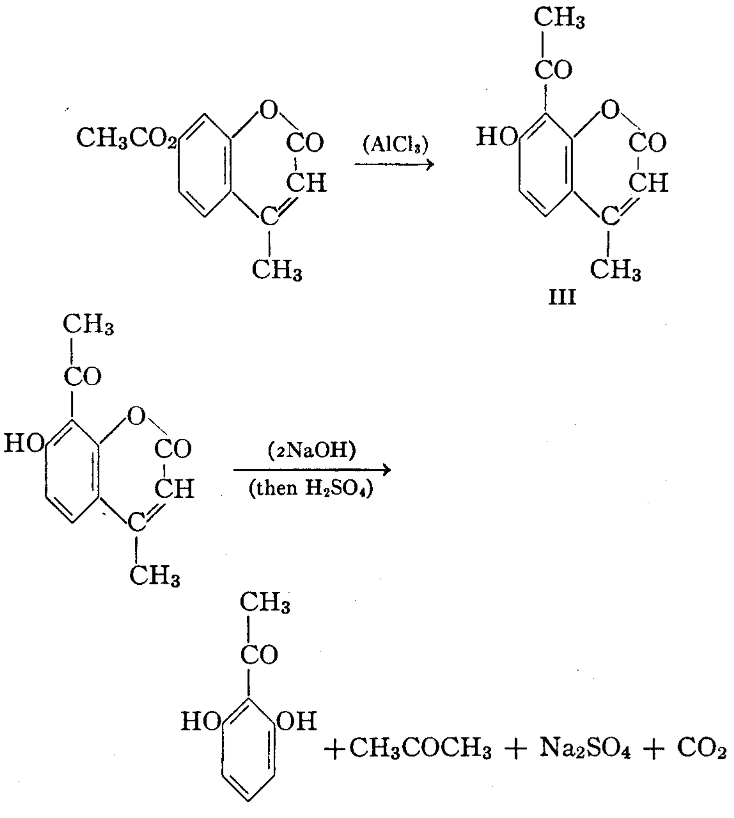
3. Methods of Preparation

1,2-Diamino-4-nitrobenzene can be prepared by the partial reduction of 2,4-dinitroaniline in alcohol solution using sodium hydrosulfide [1] or ammonium sulfide.[2,3] The method described here is a modification of that given by Kehrmann.[3]

2,6-DIHYDROXYACETOPHENONE



[1] Brand, J. prakt. Chem. (2) **74**, 471 (1907).
[2] Heim, Ber. **21**, 2305 (1888).
[3] Kehrmann, ibid. **28**, 1707 (1895).



Submitted by Alfred Russell and John R. Frye.
Checked by R. L. Shriner and Michael Witte.

1. Procedure

(*A*) 4-*Methyl-7-hydroxycoumarin* (*I*).—In a 5-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer, a thermometer reaching to the bottom, and a dropping funnel, is placed 2 l. of concentrated sulfuric acid (sp. gr. 1.84). The flask is surrounded by an ice bath, and when the temperature falls below 10° a solution of 220 g. (2 moles) of resorcinol in 260 g. (2 moles) of freshly distilled ethyl acetoacetate is added

dropwise. The mixture is stirred and the temperature kept below 10° by means of ice and salt. After all the solution has been added (about two hours) the reaction mixture is set aside for twelve to twenty-four hours without further cooling. The reaction mixture is now poured with vigorous stirring into a mixture of 4 kg. of ice and 6 l. of water. The precipitate is collected on a filter and washed with three 50-cc. portions of cold water. The crude product is then dissolved in 3 l. of 5 per cent aqueous sodium hydroxide solution, the solution filtered, and the substituted coumarin reprecipitated from the filtrate by the slow addition of dilute (1 : 10) sulfuric acid until the solution is acid to litmus. About 1100 cc. of dilute sulfuric acid is required. During the neutralization, the reaction mixture must be well stirred. The product is collected on a Büchner funnel, washed with four 50-cc. portions of cold water, and dried. The yield of 4-methyl-7-hydroxycoumarin is 290–320 g. (82–90 per cent of the theoretical amount). It is sufficiently pure for use in the next step but may be purified by recrystallization from 95 per cent ethanol using about 15 cc. of alcohol for 5 g. of product. The recrystallized material forms stout almost colorless needles melting at 185°.

(*B*) 4-*Methyl-7-acetoxycoumarin* (*II*).—A mixture of 286 g. (1.6 moles) of crude, dry 4-methyl-7-hydroxycoumarin and 572 g. (5.6 moles) of acetic anhydride is placed in a 2-l. round-bottomed flask fitted to a reflux condenser by a ground-glass joint. The mixture is refluxed for one and one-half hours, cooled to about 50°, and poured with vigorous stirring into a mixture of 4 kg. of cracked ice and 4 l. of water. The precipitate is collected on a Büchner funnel, washed with five 50-cc. portions of cold water, and spread on absorbent paper to dry. The drying is completed by placing the product in a steam oven for ten hours. The yield of crude 4-methyl-7-acetoxycoumarin is 320–340 g. (90–96 per cent of the theoretical amount). It may be purified by recrystallization from 95 per cent ethanol (5 g. of compound to 20 cc. of solvent) and forms fibrous needles melting at 150–151°. The crude oven-dried product is finely powdered and used in the next step.

(*C*) 4-*Methyl-7-hydroxy-8-acetylcoumarin* (*III*).—In a clean, dry, 5-l. round-bottomed flask are placed 200 g. (0.92 mole) of dry, powdered 4-methyl-7-acetoxycoumarin and 453 g. (3.4 moles) of technical anhydrous aluminum chloride. The flask is stoppered and shaken vigorously for three to five minutes in order to mix the ingredients thoroughly. The stopper is removed and the flask attached to a reflux condenser fitted with a gas-absorption tube (Org. Syn. **14**, 2). The flask is placed in an oil bath the temperature of which is raised quickly to 125° and then slowly over a period of two hours to 170°. At the end of this time the flask is removed from the oil bath, allowed to cool, and immersed in an ice bath. About 1 kg. of cracked ice is added, and then 2400 cc. of dilute (1 : 7) hydrochloric acid is added over a period of about two hours. The mixture is then heated on a steam bath for thirty minutes with vigorous stirring in order to effect complete decomposition. The mixture is filtered and the precipitate washed with four 50-cc. portions of cold water and sucked dry. This crude product is recrystallized by dissolving it in 4 l. of hot 95 per cent ethanol, filtering the hot solution through a warm funnel, and chilling the filtrate. The crystals are collected on a funnel and air-dried. The product melts at 162–163°, and the yield is 145–155 g. (72.5–77.0 per cent of the theoretical amount) (Note 1).

(*D*) 2,6-*Dihydroxyacetophenone* (*IV*).—A 5-l. three-necked, round-bottomed flask is fitted with a reflux condenser, a dropping funnel, and a glass tube, extending to the bottom of the flask, connected to a cylinder of nitrogen (Note 2). In the flask are placed 148 g. (0.68 mole) of 4-methyl-7-hydroxy-8-acetylcoumarin and 500 cc. of distilled water. A rapid stream of nitrogen is bubbled through the water suspension until all the air in the apparatus is displaced, and then a slow stream of the gas is kept passing through the solution (Note 3). A solution of 129 g. (3.23 moles) of sodium hydroxide in 580 cc. of water is added through the dropping funnel and the mixture heated on a steam bath for five hours. The solution is then cooled and acidified by the addition of about 1 l. of dilute (1 : 3) hydrochloric acid. The stream of nitrogen gas is continued through-

out the period of heating and while the solution is cooling. It may be stopped after the solution is acid. The crude 2,6-dihydroxyacetophenone which separates on acidification is collected on a filter, washed three times with 50-cc. portions of cold water, and air-dried. A yield of 90–95 g. (87–92 per cent of the theoretical amount based on the 4-methyl-7-hydroxy-8-acetylcoumarin) of light yellow solid is obtained.

The purification is accomplished by dissolving the crude product in 1 l. of 95 per cent ethanol, adding 20 g. of Norite, and heating the mixture on a steam cone for fifteen minutes with occasional shaking. After this time, 800 cc. of warm water is added, and the solution is heated five more minutes and filtered through a hot funnel. The greenish filtrate is chilled in an ice-salt bath, and the first crop (about 65 g.) of lemon-yellow needles of 2,6-dihydroxyacetophenone is removed by filtration. The filtrate is then concentrated under reduced pressure to a volume of 800 cc., again chilled, and the second crop of product (about 15 g.) collected on a filter. The total yield of purified 2,6-dihydroxyacetophenone, melting at 154–155°, is 75–85 g. (a recovery of 83–89 per cent) (Note 4).

2. Notes

1. The mother liquor from this crystallization contains the isomeric acetyl derivative, 4-methyl-6-acetyl-7-hydroxycoumarin.

2. Hydrogen or illuminating gas may be used in place of nitrogen, provided that proper precautions are taken to conduct the gas from the condenser to a flue.

3. It is important to prevent oxygen from coming in contact with the alkaline solution of the 2,6-dihydroxyacetophenone since it causes the formation of oxidation products which materially lower the yield and cause difficulty in purification. The inert atmosphere must be maintained until after the mixture is acidified.

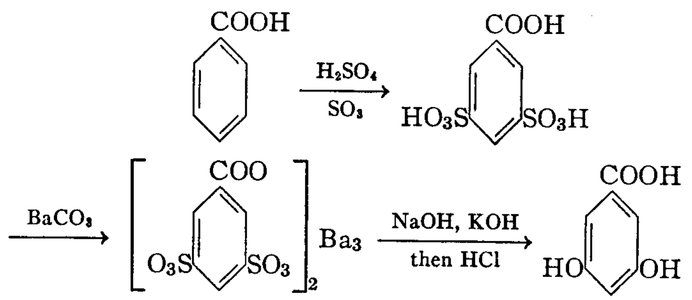
4. The first two steps in this preparation have been carried out using four times the quantities stated with no reduction in the yields. The third step, involving the Fries rearrangement, usually gives lower yields when larger amounts are used. The amounts of materials in the fourth step may be doubled.

3. Methods of Preparation

2,6-Dihydroxyacetophenone has been prepared by the action of methylmagnesium iodide on 2,6-dimethoxybenzonitrile [1] followed by cleavage of the ether linkages with aluminum chloride. The present method is based on the procedures described by Limaye [2] and by Baker.[3]

3,5-DIHYDROXYBENZOIC ACID

(α-Resorcylic Acid)



Submitted by Arthur W. Weston and C. M. Suter.
Checked by C. F. H. Allen and John W. Gates, Jr.

1. Procedure

To 200 g. (1.64 moles) of benzoic acid in a 1-l. Kjeldahl flask, in the top of which is inserted a loosely fitting cold finger (Note 1), is added 500 cc. of fuming sulfuric acid (Note 2). The mixture is heated in an oil bath for five hours at 240–250° (bath temperature).

After standing overnight the syrupy liquid is poured slowly with stirring into 3 kg. of ice in a 3-gal. crock (Note 3). The

[1] Mauthner, J. prakt. Chem. **139**, 290 (1934).
[2] Limaye, Ber. **67**, 12 (1934).
[3] Baker, J. Chem. Soc. **1934**, 1953.

solution is then neutralized by adding barium carbonate in 100-g. portions, stirring occasionally until the gas evolution slackens before each addition: 2400–2500 g. is required. The pasty mass is filtered by suction on a 30-cm. Büchner funnel, and the barium sulfate is washed with five 300-cc. portions of water. The combined filtrates are evaporated nearly to dryness on a steam bath and finally dried in an oven at 125–140° (Note 4). The yield of crude barium salt is 640–800 g.

The operator should wear goggles and long-sleeved gloves during the next two operations. The dried, pulverized barium salt is introduced in 200-g. portions into a melt of 600 g. each of sodium and potassium hydroxides contained in a 14 by 20 cm. copper beaker. The mixture is stirred with a copper stirrer and the temperature determined with a thermometer in a copper well (Note 5). Each portion is well stirred in before the next is added. The temperature is then slowly raised to 250–260°, at which point a vigorous reaction occurs with copious evolution of gas. After this has slackened (about one-half hour) the temperature is raised to 280–310° and maintained there for one hour, then allowed to drop to 200°. The melt is ladled into 6 l. of water (Notes 6 and 7). The barium sulfite is filtered by suction, and the filtrate is acidified with concentrated hydrochloric acid (about 2.5 l. is required).

The resulting solution (about 9 l.) is divided into two portions and each is extracted three times, 600 cc. of ether being used each time (Note 8). The combined extracts are concentrated to about 1 l. and dried overnight over 150 g. of anhydrous sodium sulfate. After filtration and evaporation of the ether, there remains 137–160 g. (58–65 per cent of the theoretical amount) of a slightly colored product, melting with decomposition at 227–229°. It is sufficiently pure for most purposes (Notes 9 and 10).

2. Notes

1. An ordinary glass funnel suspended in the neck serves less satisfactorily, whereas with a water condenser solidification of the sulfur trioxide causes difficulty.

2. This acid, approximately 30 per cent sulfur trioxide, is made by mixing 500 g. each of fuming sulfuric acid containing 60 per cent free sulfur trioxide and concentrated sulfuric acid (sp. gr. 1.84); 500 cc. of this mixture is used.

3. The reaction product may solidify at first, but it dissolves later.

4. The evaporation of the solution is most conveniently done overnight. The final drying is best done in flat metal trays, and the length of time required depends upon the temperature. The checkers left trays on a steam coil over a week end.

5. An 18-cm. piece of 10 to 12-mm. copper tubing, pounded together at the lower end, is used. The stirrer can be made of the same tubing.

6. The addition of the hot melt causes some spattering.

7. Alternatively, the melt may be poured into shallow metal trays and allowed to cool and solidify. It is then pulverized and dissolved. Grinding is difficult and unpleasant. The melt should not be allowed to solidify in the reaction vessel.

8. A large automatic extraction apparatus may be used if available.

9. The color can be removed by recrystallization from hot acetic acid, using a decolorizing carbon. A solution of 16 g. of the crude acid in 85 cc. of hot acetic acid deposits 13.4 g. of white needles after filtration through a 2-mm. layer of Darco in a hot funnel and cooling. These are anhydrous after drying at 100° at 35 mm. for two hours; m.p. 234–235° with decomposition (corr.). The melting point varies with the rate of heating.

10. This material is partially hydrated.[1] The melting point is unchanged after recrystallization from water.

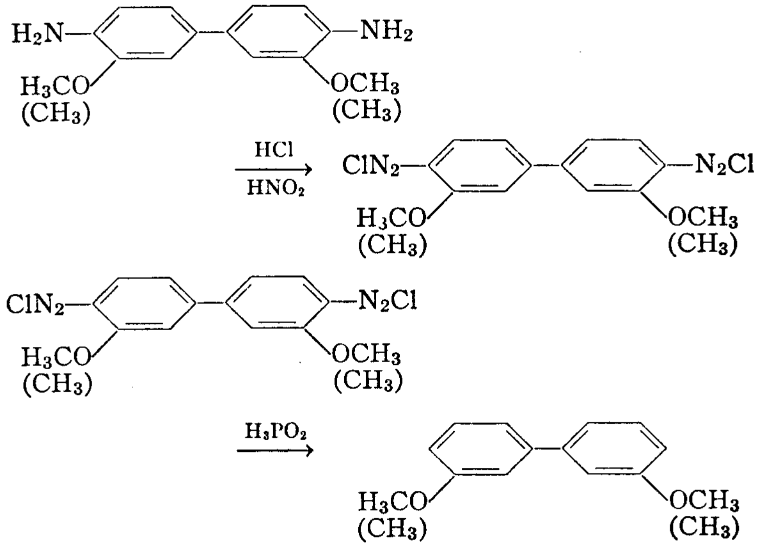
3. Methods of Preparation

3,5-Dihydroxybenzoic acid is most conveniently prepared by alkaline fusion of the disulfonic acid obtained by sulfonation of benzoic acid.[1,2,3] It has also been prepared by alkaline fusion

[1] Barth and Senhoefer, Ann. **159**, 222 (1871); **164**, 109 (1872).
[2] Graves and Adams, J. Am. Chem. Soc. **45**, 2439 (1923).
[3] Hohenemser, Ber. **35**, 2305 (1902).

of the 3,5-dihalobenzoic acids[4,5] or of 3-bromo-5-sulfobenzoic acid.[6] Benzoic acid has been sulfonated using various strengths of sulfuric acid with or without catalysts.[7]

3,3′-DIMETHOXYBIPHENYL AND 3,3′-DIMETHYLBIPHENYL



Submitted by NATHAN KORNBLUM.
Checked by W. E. BACHMANN and S. KUSHNER.

1. Procedure

(*A*) *3,3′-Dimethoxybiphenyl.*—In a 1.5-l. beaker are placed 400 cc. of water and 31 cc. of concentrated hydrochloric acid (sp. gr. 1.19). This solution is heated to boiling, the flame is

[4] Ger. pat. 286,266 [Frdl. **12**, 158 (1914–1916)].
[5] U. S. pat. 1,321,271 [C. A. **14**, 186 (1920)].
[6] Böttinger, Ber. **8**, 4 (1875); **9**, 180 (1876); Bülow and Riess, ibid. **35**, 3901 (1902); Koller and Klein, Monatsh. **64**, 85 (1935).
[7] Herzig and Epstein, Monatsh. **29**, 661 (1901); Brunner, ibid. **50**, 216 (1928); Lock and Nottes, ibid. **68**, 51 (1936); Suter and Weston, J. Am. Chem. Soc. **61**, 232 (1939).

removed, and 40 g. (0.16 mole) of *o*-dianisidine (Note 1) is added. The hot mixture is stirred for about three minutes, until only a small amount of solid remains. The beaker is then placed in an ice-salt mixture and its contents stirred mechanically until the temperature has dropped to about 15°. At this point 35 cc. more of concentrated hydrochloric acid is added. When the temperature of the mixture has fallen to 10–13°, a solution of 23.3 g. (0.33 mole) of 97 per cent sodium nitrite (or an equivalent amount of sodium nitrite of higher or lower purity) in 50 cc. of water is added from a dropping funnel in the course of ten to fifteen minutes. The contents of the beaker are then stirred for fifteen to twenty minutes at 5–10°, and finally filtered rapidly with suction from an appreciable amount of dark material (Note 2).

The cold, clear red filtrate is now poured rapidly into a 2-l. flask containing 325 cc. of ice-cold 30 per cent hypophosphorous acid solution (Note 3). Immediate evolution of nitrogen occurs. The flask is stoppered loosely, placed in a refrigerator for eight or ten hours, and then allowed to stand at room temperature for another eight to ten hours (Note 4). The reaction product is transferred to a 2-l. separatory funnel, and the lower dark brown layer is separated from the aqueous phase. The aqueous layer is extracted with two 125-cc. portions of ether (Note 5). The brown oil combined with the ether extracts is washed in a separatory funnel with two 30-cc. portions of 20 per cent sodium hydroxide solution (Note 6). Separation into two layers occurs rapidly, but occasionally the aqueous phase will remain turbid for some time. The loss by discarding the turbid sodium hydroxide washings is negligible. The ether solution is dried with a minimal amount of anhydrous potassium carbonate, 5 g. usually being sufficient (Note 7).

After filtration of the ether solution from the mixture of solid potassium carbonate and dark solids which have settled out, the ether is removed by distillation on a steam cone from a 50-cc. modified Claisen flask having a 15-cm. column. Usually suction must be applied to remove the last traces of ether. The residue is distilled at 4 mm. and a bath temperature of 200°. There is a

small fore-run of 1–1.5 g. of a very pale yellow liquid which distils at 155–157°. The main fraction, boiling at 157–159°, is practically colorless and weighs 19–22 g. When the temperature of the thermometer in the flask starts to drop, the bath temperature is gradually raised to 240°. In this way, 3–4 g. more of light orange-yellow dianisyl is obtained. The yield based on the three fractions is 23–27.5 g. (66–78 per cent of the theoretical amount). The fractions usually crystallize spontaneously; if they do not crystallize, they are cooled and scratched.

The main fraction melts at 41–43° (Note 8), and the other two fractions usually melt about a degree or two lower. The product is pure enough for most purposes; it may be recrystallized from the minimal volume of alcohol necessary for solution at 45–50°. The solution is cooled to about 35°; any oil which precipitates is brought back into solution by cautious addition of alcohol. The saturated solution is seeded, allowed to cool to room temperature, and then kept in a refrigerator for at least four hours. In this manner, 20–21 g. of flat, colorless needles is obtained; the product melts at 42–43.5°.

(*B*) 3,3′-*Dimethylbiphenyl*.—Twenty-seven grams (0.13 mole) of *o*-tolidine (Note 9) is tetrazotized according to Org. Syn. **16**, 12. It is not necessary to take the indicated precautions against a slight excess of nitrous acid. The clear orange tetrazonium solution is added to 290 cc. of 30 per cent hypophosphorous acid (Note 10), and the mixture is allowed to stand, loosely stoppered, at room temperature for sixteen to eighteen hours (Note 11).

The reaction product is transferred to a 2-l. separatory funnel, and the red oily layer is separated from the aqueous phase. The aqueous layer is extracted once with 60 cc. of benzene. The combined red oil and benzene extract are dried with 1–5 g. of anhydrous sodium sulfate (Note 12). The benzene is removed by distillation from a 50-cc. modified Claisen flask having a 15-cm. column. The flask is heated in an oil bath to a final temperature of about 150° to insure removal of the last traces of benzene. The residue is distilled at 3 mm. and a bath temperature of 155°. A practically colorless fore-run of 1–1.5 g. comes

over from 109° to 114°. This is followed by 15.5–16 g. of a very pale lemon-yellow liquid which boils at 114–115°. When the temperature of the thermometer in the flask starts to fall, the bath temperature is raised to 170°, and an additional 1–1.5 g. of light lemon-yellow material is obtained (Note 13). The total yield is 17.5–19 g. (76–82 per cent of the theoretical amount) (Notes 14 and 15).

2. Notes

1. Eastman Kodak Company's technical grade, melting at 133–135°, was used.

2. Usually the pores of the filter paper become partially clogged after about half of the mixture has been filtered so that the rate of filtration is cut down considerably. In this event a fresh funnel and filter should be employed.

3. When less hypophosphorous acid solution is used, the yields are slightly lower, the product more highly colored than that obtained here, and the reaction time appreciably greater. When large amounts of a cheap amine are to be deaminated, it might be worth while to investigate the use of less hypophosphorous acid. In one run, 645 cc. of hypophosphorous acid solution was used for 40 g. of dianisidine. The yield was 29 g. (83 per cent of the theoretical amount). With valuable amines it is probably best to use more hypophosphorous acid than is called for in these directions. Thus, in deaminating 33 g. of 2,2′-dimethyl-4,4′-diamino-5,5′-dimethoxybiphenyl, 1200 cc. of 30 per cent hypophosphorous acid was used. There was obtained 24.5 g. (83 per cent of the theoretical amount) of purified 2,2′-dimethyl-5,5′-dimethoxybiphenyl.

4. If the flask is permitted to stand at room temperature directly after the two solutions are mixed, the yield is a little lower than that obtained with these directions and the product is somewhat more highly colored. The entire reaction may be run at refrigerator temperature, in which event twenty-five to thirty hours should elapse before the product is worked up.

When this reaction is applied to aniline derivatives, it appears advisable to conduct it entirely at refrigerator temperature

owing to lowered thermal stability of the diazonium compounds as compared to the tetrazonium salts obtained from the benzidine type.

5. If the entire reaction is carried out at refrigerator temperatures the crude product is a light brown solid, which is best worked up by filtering with suction, dissolving in ether, and proceeding as in the regular directions.

6. When this washing is omitted, the product contains a white, alkali-soluble solid and rapidly becomes orange-brown in color.

7. The potassium carbonate usually retains some dianisyl. It should be washed with a little of the ether which has been distilled off, and these washings redistilled.

8. In agreement with others, the checkers obtained a product melting at 31.5–33.5°. After recrystallization from alcohol, the 3,3′-dimethoxybiphenyl melted at 33.5–35°. This low-melting form changed rapidly to the form melting at 42–43.5° when a solution or melt of the former or even the solid came in contact with a crystal of the high-melting form (obtained from the submitter).

9. Eastman Kodak Company's *o*-tolidine, m.p. 128–129°, was used.

10. Use of 175 cc. of hypophosphorous acid gave a yield of 17.8 g. (77 per cent of the theoretical amount). The first and last fractions were turbid.

11. The yield and quality of the product are identical with those obtained by conducting the reaction at refrigerator temperature.

12. Washing the benzene solution with aqueous alkali was found to be unnecessary.

13. In spite of the slight differences in color, the three fractions have almost identical refractive indices ($n_D^{20°}$ 1.5945).

14. One run was made using 27 g. of Eastman's practical *o*-tolidine, m.p. 121–125°. The procedure employed differed from the above only in that the benzene solution was washed once with 40 cc. of 10 per cent aqueous alkali. There was obtained 18.9 g. (82 per cent of the theoretical amount) of a light orange-yellow liquid possessing essentially the same refractive index as the product obtained from the better grade of *o*-tolidine.

15. This method of deaminating aromatic amines appears to be of general applicability, particularly to benzidine and its derivatives. Benzidine itself has been deaminated in 60 per cent yield. The use of hypophosphorous acid in preference to alcohol for these deaminations arises from the fact that this procedure is much simpler, the yields are higher, and the products are of better quality.

This use of hypophosphorous acid for the deamination of aromatic amines appears to have originated with Mai.[1] Recently it has been used for this purpose by Raiford and Oberst.[2]

3. Methods of Preparation

3,3′-Dimethoxybiphenyl has been prepared by methylating 3,3′-dihydroxybiphenyl with methyl iodide[3] or dimethyl sulfate;[4] and by deaminating tetrazotized *o*-dianisidine with alcohol.[5,6,7] The present procedure is a slight modification of Mai's directions.

3,3′-Dimethylbiphenyl can be prepared from *m*-bromotoluene[8] or *m*-iodotoluene[9] and sodium; by the action of copper powder on *m*-iodotoluene;[10] by treating 4,4′-dihydroxy-3,3′-dimethylbiphenyl with zinc dust;[11] by heating 4,4′-dichloro-3,3′-dimethylbiphenyl with hydriodic acid and phosphorus;[11] by treating *o*-tolidine with nitrous acid in alcoholic solution;[12] by the decomposition of tetrazotized *o*-tolidine with methanol or ethanol

[1] Mai, Ber. **35**, 162 (1902).
[2] Raiford and Oberst, Am. J. Pharm. **107**, 242 (1935) [C. A. **29**, 6216 (1935)].
[3] Barth, Ann. **156**, 98 (1870).
[4] Schultz and Kohlhaus, Ber. **39**, 3343 (1906).
[5] Starke, J. prakt. Chem. (2) **59**, 226 (1899).
[6] Haeussermann and Teichmann, Ber. **27**, 2108 (1894).
[7] Mascarelli and Visintin, Gazz. chim. ital. **62**, 358 (1932).
[8] Perrier, Bull. soc. chim. (3) **7**, 182 (1892).
[9] Schultz, Rohde, and Vicari, Ber. **37**, 1401 (1904); Ann. **352**, 112 (1907).
[10] Ullmann and Meyer, Ann. **332**, 43 (1904).
[11] Stolle, Ber. **21**, 1096 (1888).
[12] Schultz, ibid. **17**, 468 (1884).

in the presence of zinc dust.[13,14] It has recently been prepared by reduction of *m*-bromotoluene with hydrazine hydrate, using a palladium-calcium carbonate catalyst.[15] Upon treatment of lithium *m*-tolyl with oxygen, a small amount of 3,3′-dimethylbiphenyl is formed.[16]

n-DODECYL (LAURYL) MERCAPTAN

$$n\text{-}C_{12}H_{25}Br + S{=}C(NH_2)_2 \rightarrow C_{12}H_{25}{-}S{-}C\Big\langle{}^{NH}_{NH_2} \cdot HBr$$

$$2C_{12}H_{25}S{-}C\Big\langle{}^{NH}_{NH_2} \cdot HBr + 2NaOH \rightarrow$$

$$2C_{12}H_{25}SH + H_2N{-}\overset{\overset{\textstyle NH}{\|}}{C}{-}NHCN + 2NaBr + 2H_2O$$

Submitted by G. G. Urquhart, J. W. Gates, Jr., and Ralph Connor.
Checked by Lee Irvin Smith, R. T. Arnold, and Kenneth Stevenson.

1. Procedure

A mixture of 125 g. (0.5 mole) of *n*-dodecyl bromide (Note 1), 38 g. (0.5 mole) of thiourea, and 250 cc. of 95 per cent ethyl alcohol is refluxed on a steam cone for three hours (Notes 2, 3, and 4). A solution of 30 g. (0.75 mole) of sodium hydroxide in 300 cc. of water is added, and the mixture is refluxed for two hours. During this period the mercaptan separates as a pink to red oil. The layers are separated, and the aqueous layer is acidified with dilute sulfuric acid (7 cc. of concentrated acid to 50 cc. of water) and then extracted with one 75-cc. portion of benzene (Note 5). The extract is added to the crude mercaptan layer, and the whole is washed twice with 200-cc. portions of water and

[13] Winston, Am. Chem. J. **31**, 128 (1904).
[14] Schlenk and Brauns, Ber. **48**, 666 (1915).
[15] Busch, Hahn, and Mathauser, J. prakt. Chem. **146**, 22 (1936).
[16] Müller and Töpel, Ber. **72**, 273 (1939).

then dried over 20 g. of anhydrous sodium sulfate (Note 6). The solvent is removed and the residual oil distilled from a modified Claisen flask. There is no appreciable fore-run (Note 6). The yield of *n*-dodecyl mercaptan, b.p. 165–169°/39 mm., is 80–84 g. (79–83 per cent of the theoretical amount) (Notes 7 and 8).

2. Notes

1. The preparation of lauryl bromide has been described (Org. Syn. Coll. Vol. 1, 27), but the following modification avoids the emulsion formed in washing lauryl bromide with sulfuric acid. The crude bromide from the reaction mixture is washed thoroughly with water and then with potassium carbonate solution. The washing with water must be thorough enough to remove most of the acid in order to prevent the formation of heavy foam by the carbonate. The bromide is then dried over calcium chloride and distilled. The distillate is washed with concentrated sulfuric acid and treated as described (loc. cit.). The checkers, however, found the method using anhydrous hydrogen bromide (Org. Syn. **15**, 24) to be preferable.

2. The intermediate laurylisothiourea hydrobromide may be obtained by cooling the alcohol solution in ice and filtering the precipitate. It may be further purified by washing with ether. An alternative method gives more satisfactory results. The alcohol solution is diluted with 150 cc. of water and heated until the solution is homogeneous and then, after cooling slightly, 200 cc. of concentrated hydrochloric acid is added; the laurylisothiourea hydrochloride separates quantitatively as a waxy white solid.

3. The reflux period required for complete reaction varies considerably with the structure of the halide. Some alkyl bromides require more than three hours. Alkyl chlorides frequently require sixteen hours and occasionally as much as twenty-four hours.

4. This procedure is useful for the preparation of other mercaptans. The yields are of the same order. The boiling points are as follows:

n-Heptyl		174–176°
n-Octyl	198–200°;	98–100°/22 mm.
n-Nonyl	220–222°;	98–100°/15 mm.
n-Decyl	88– 91°/2 mm.;	96–97°/5 mm.
n-Undecyl		103–104°/3 mm.
n-Octadecyl		170–175°/4 mm.

5. While benzene is the most satisfactory solvent for this extraction, emulsions are sometimes produced when it is used for the extraction of other mercaptans. To obviate this difficulty the same amount of ether may be used, provided that the alcohol is first removed by distillation on a steam bath.

6. If the ether extracts are not thoroughly dry, the mercaptan appears slightly cloudy on subsequent distillation. The checkers found that this cloudiness was frequently due to colloidal sulfur. The sulfur can be removed by shaking an ether solution of the cloudy product with bone black, then filtering and distilling.

7. The odor of lauryl mercaptan is not disagreeable, and no unusual precautions need be taken in working with it. With lower-molecular-weight mercaptans a trap containing alkaline potassium permanganate solution will prevent the escape of unpleasant odors.

8. Other boiling points: 107–109°/2 mm.; 133–135°/7 mm.; 145–147°/15 mm.; 150–152°/20 mm.; 158–160°/28 mm.; 168–170°/38 mm.

3. Methods of Preparation

n-Dodecyl mercaptan has been prepared by the action of alkali on the salts of *S*-*n*-dodecyl thiourea [1] and by reduction of di-*n*-dodecyl disulfide.[2,3]

[1] Backer, Terpstra, and Dijkstra, Rec. trav. chim. **51**, 1166 (1932).
[2] Noller and Gordon, J. Am. Chem. Soc. **55**, 1090 (1933).
[3] Henkel et Cie., Fr. pat. 751,117; U. S. pat. 2,031,529 [C. A. **30**, 2202 (1936)].

DYPNONE

$$2C_6H_5COCH_3 \xrightarrow{Al[OC(CH_3)_3]_3} C_6H_5(CH_3)C{=}CHCOC_6H_5 + H_2O$$

Submitted by Winston Wayne and Homer Adkins.
Checked by Nathan L. Drake, Wm. H. Souder, Jr., and Ralph Mozingo.

1. Procedure

In a 1-l. round-bottomed, three-necked flask, fitted with a thermometer, an efficient mechanical stirrer (Note 1), and a 35-cm. Vigreux column fitted to a condenser and receiver protected by a calcium chloride tube, are placed 345 g. (400 cc.) of dry xylene, 120 g. (117 cc., 1 mole) of dry acetophenone, and 135 g. (0.55 mole) of aluminum *tert.*-butoxide (p. 8) (Note 2). The stirrer is started and the flask heated in an oil bath so that the temperature of the reaction mixture is held between 133° and 137°. *tert.*-Butyl alcohol slowly distils at a temperature in the vapor of 80–85°. The distillation of the alcohol can be accomplished by maintaining the temperature of the heating bath between 150° and 155° for two hours after distillation has commenced (Notes 3 and 4).

The reaction mixture is cooled to 100°, and 40 cc. of water is added cautiously in small portions with continued stirring. As the water is added the mixture sets to a gel, and then, upon the addition of the remainder of the water and gentle tapping of the reaction flask, the stiff mass breaks up and boiling begins. Refluxing is continued by heating the oil bath for another fifteen minutes to ensure the complete hydrolysis of the aluminum *tert.*-butoxide.

After cooling, the reaction mixture is transferred in nearly equal portions to four centrifuge bottles and the aluminum hydroxide is centrifuged out (Note 5). The upper liquid layer is removed and the aluminum hydroxide is worked up to a smooth paste, by means of a spatula, with a total of approximately 250 cc. of ether for the four portions. The aluminum hydroxide is again centrifuged out and the ether extract poured off. The

centrifuging is repeated three more times so that approximately a liter of ether is used to separate the product from the aluminum hydroxide (Note 6).

Ether and *tert.*-butyl alcohol are removed by distillation at atmospheric pressure without a column, and the xylene is removed by distillation through a 35-cm. Vigreux column at 25–50 mm. The residue is transferred to a smaller flask, and the acetophenone is first distilled at about 80°/10 mm., and finally the dypnone is distilled at 150–155°/1 mm. (Notes 7 and 8). The yield is 85–91 g. (77–82 per cent of the theoretical amount) of a yellow liquid.

2. Notes

1. Instead of the customary mercury seal, a simple rubber tube seal suggested by Dr. L. P. Kyrides is recommended. The upper end of an 8-cm. length of 10-mm. glass tubing, projecting through a stopper, is fitted with a 2-cm. piece of 6-mm. rubber tubing so that it projects 5 mm. beyond the end of the glass tube. This projecting portion fits snugly to form a seal round an 8-mm. stirrer shaft running through the glass tubing. Glycerol is applied at the point of contact of glass and rubber to act as a lubricant and sealing medium. This type of seal can be conveniently used with reduced pressure down to 10 mm.

2. Slightly more than a mole of aluminum *tert.*-butoxide is used for each mole of water split out as the alkoxide loses its effectiveness after the replacement of one alkoxyl by an hydroxyl group.

3. The reaction may proceed so vigorously at first that the distillation temperature will rise to 100° or above. This is not detrimental and the temperature will soon fall.

4. As the reaction proceeds the color changes from yellow to deep orange and the mixture becomes viscous. After about forty-five minutes the distillation temperature begins to fall and eventually reaches 70° owing to the formation of butylene from the aluminum *tert.*-butoxide which decomposes slightly at this temperature.

5. Ordinary undried ether is used in balancing the centrifuge bottles, in removing any aluminum hydroxide and product remaining in the flask, and in the subsequent extraction of the aluminum hydroxide.

6. This method eliminates the washing and drying of the customary extraction procedure. The small amount of water present distils off with the solvent. The extraction should be done carefully and thoroughly. If it has been carried out properly the aluminum hydroxide will be white or faintly yellow and at least 95 per cent of the original acetophenone can be accounted for after the final distillation.

7. The acetophenone and dypnone are easily separated in any of the common types of fractionating columns. The column should be short (12 to 18 cm.) and electrically heated because of the high boiling point of the product. An undistillable residue of 5–10 g. remains.

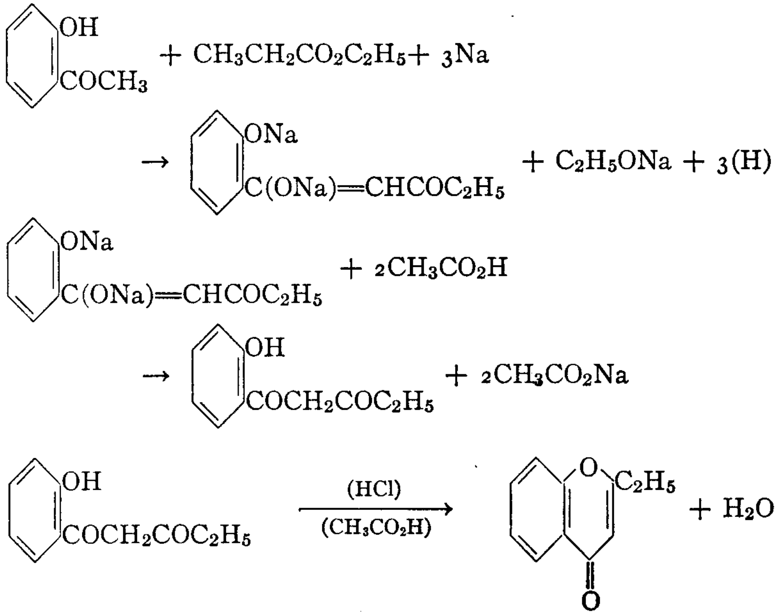
8. The boiling point varies greatly with the rate of distillation and the amount of ebullition.

3. Methods of Preparation

Dypnone has been prepared by the action of sodium ethoxide,[1] aluminum bromide,[2] phosphorus pentachloride,[3] aluminum triphenyl,[4] zinc diethyl,[5] calcium hydroxide,[6] anhydrous hydrogen chloride,[5,7] aluminum chloride,[4] and aluminum *tert.*-butoxide[8] on acetophenone. It has been prepared by the action of aniline hydrochloride on acetophenone anil followed by treatment with hydrochloric acid.[9] The preparation of aluminum *tert.*-butoxide has been described[8,10] (p. 8). The procedure described is a modification of that by Adkins and Cox.[8]

[1] Eijkman, Chem. Weekblad **1**, 349 (1904).
[2] Konowalow and Finogejew, J. Russ. Phys. Chem. Soc. **34**, 944 (1902) [Chem. Zentr. **74**, I, 521 (1903)].
[3] Taylor, J. Chem. Soc. **1937**, 304.
[4] Calloway and Green, J. Am. Chem. Soc. **59**, 809 (1937).
[5] Henrich and Wirth, Monatsh. **25**, 423 (1904).
[6] Porlezza and Gatti, Gazz. chim. ital. **56**, 265 (1926).
[7] Delacre, Bull. classe sci. Acad. roy. Belg. (3) **20**, 467 (1898); Colonge, Bull. soc. chim. (4) **49**, 426 (1931); Kohler, Am. Chem. J. **31**, 642 (1904).
[8] Adkins and Cox, J. Am. Chem. Soc. **60**, 1151 (1938).
[9] Reddelien, Ber. **46**, 2712 (1913).
[10] Oppenauer, Rec. trav. chim. **56**, 137 (1937).

2-ETHYLCHROMONE



Submitted by Ralph Mozingo.
Checked by Homer Adkins and Robert J. Gander.

1. Procedure

In a 1-l. three-necked flask fitted (Note 1) with a reflux condenser, a dropping funnel, and a stirrer (Note 2) are placed 24 g. (1.05 gram atoms) of oxide-free sodium and 200 cc. of xylene (Note 3). The condenser is protected by a drying tube containing soda-lime. The flask is surrounded by an oil bath which is heated until the sodium is melted. The stirrer is started, and, after the sodium is powdered, the oil bath is removed. When the contents of the flask have cooled to room temperature, the stirrer is stopped, the xylene decanted, and the sodium washed with 100 cc. of dry ether to remove traces of xylene.

The flask is replaced and completely surrounded by an ice bath (Note 4). A current of nitrogen is passed through the flask

for five minutes by means of a rubber tube attached to the dropping funnel. The nitrogen inlet tube is removed, and a mixture of 60 g. (0.44 mole) of *o*-hydroxyacetophenone (Note 5) and 125 g. (140 cc., 1.2 moles) of ethyl propionate (Note 3) is placed in the dropping funnel and protected by a soda-lime tube. The ester-ketone mixture is dropped very slowly onto the powdered sodium. After a small amount (2–5 cc.) of the mixture has been added, the ice bath is removed and the flask warmed with the hand to make sure that the reaction has started (Note 6). When the reaction has started, the funnel is adjusted so that one-half of the ester-ketone mixture is added over a period of one and one-half to two hours. After half of the mixture has been added, the rate of addition is again regulated so that the remainder is added in one-half hour.

After all the ester-ketone mixture has been added and the reaction has subsided, the ice bath is removed and replaced by a steam bath. The crust on the mixture is broken up and the mixture heated on a steam bath until all the sodium has reacted (thirty to sixty minutes). The reaction mixture is allowed to cool and is poured with stirring onto 300 g. of crushed ice. Ninety-five cubic centimeters of glacial acetic acid in 350 cc. of water is added, and the mixture is stirred for half an hour. The organic layer which separates is removed by means of a separatory funnel, and the water layer is extracted three times with 200-cc. portions of ether. The extracts are combined with the original organic material, and the ether is distilled from a steam bath. To the residue are added 150 cc. of glacial acetic acid and 10 cc. of concentrated hydrochloric acid, and the solution is refluxed for thirty minutes, after which it is allowed to cool to room temperature (Note 7).

The entire reaction mixture is then subjected to fractional distillation through a Widmer column (Note 8). The material boiling up to 120° is removed at atmospheric pressure and discarded. The contents of the flask are cooled and the pressure reduced to 7 mm. The fraction up to 80°/7 mm. is removed and discarded. The material boiling at 80–90°/7 mm. is collected, and, after the contents of the flask have been cooled, the

pressure is reduced to 2 mm. and all the material boiling up to 110°/2 mm. is collected and combined with the 80–90°/7 mm. fraction. The next fraction, boiling at 110–138°/2 mm., is collected separately. On refractionation of the lower fraction (b.p. 80°/7 mm.–110°/2 mm.) there is obtained 13–15 g. of *o*-hydroxyacetophenone (b.p. 87–88°/7 mm.). To the residue after recovery of the *o*-hydroxyacetophenone is added the fraction boiling at 110–138°/2 mm. The pressure is again reduced to 2 mm. and the fraction boiling at 124–126°/2 mm. collected. This fraction is pure 2-ethylchromone and weighs 42–45 g. (70–75 per cent of the theoretical amount based on the ketone not recovered) (Note 9).

2. Notes

1. All the stoppers used should be rubber ones that have been boiled for two hours in 10 per cent sodium hydroxide and thoroughly washed and dried before use.

2. A convenient stirrer may be made by fitting a ¼-in. brass rod with a disc 1 in. in diameter. Four holes are drilled through the disc, and through each hole is placed a loop of 18-gauge nichrome wire. The loops are each turned so that the twisted end is next to the stirrer shaft and each is twisted in the middle to give a double loop. The stirrer shaft is then passed through a 4-in. length of glass tubing which fits tightly about the shaft. A rubber seal is made by slipping a piece of rubber tubing over the brass rod and glass tubing. The rubber tubing extends about 3 mm. up onto the stirrer shaft, over which it fits rather tightly. A drop of glycerol placed on the stirrer shaft just above the rubber sleeve serves as a lubricant for the seal. The seal is similar to that described for the preparation of dypnone (p. 40, Note 1).

3. The xylene is dried over sodium and distilled from it. The ethyl propionate is dried over phosphorus pentoxide, more of the drying agent being added from time to time until some solid phosphorus pentoxide remains. The ester is then decanted into a flask containing fresh phosphorus pentoxide and fractionated. The fraction boiling at 98–99°/745 mm. is collected.

4. An ice bath is used to keep the reaction from becoming too violent. An ice-salt bath must not be used or the reaction may be delayed in starting.

5. The *o*-hydroxyacetophenone was made as described by Miller and Hartung (Org. Syn. **13**, 90) for *o*- and *p*-propiophenone except that the procedure for isolating the product was modified as follows. The cold partly solidified oil, separating after acidification, was diluted with benzene and the water layer extracted with benzene. After distillation of the benzene, the residue was distilled at 17 mm. until the solid *p*-isomer began to collect in the condenser. The distillate was then fractionated through a Widmer column, and the fraction boiling at 90–110°/17 mm. was saved. Refractionation gave *o*-hydroxyacetophenone boiling at 105–106°/20 mm. or 87–88°/7 mm. in a yield of 30 per cent based upon the phenyl acetate.

6. It is *very important* that the operator assure himself that the reaction has started before more of the ester-ketone mixture is added, and that the first half of the mixture be added slowly, or the reaction may proceed with *explosive violence.* It is usually possible to tell when the reaction has started by the local evolution of heat when the ice bath is removed and by the appearance of the yellow salt of the diketone.

7. The preparation should be carried as far as this point without interruption.

8. The Widmer column had a spiral 15 cm. in length, and had an electrically heated jacket.[1]

9. The submitter carried out this preparation with twice the quantities recommended here. The yield was 68–77 g. (56–64 per cent of the theoretical amount).

3. Methods of Preparation

This chromone has been prepared by the condensation of ethyl propionate with *o*-hydroxyacetophenone using sodium.[2,3]

[1] Smith and Adkins, J. Am. Chem. Soc. **60**, 662 (1938).
[2] Heilbron, Hey, and Lowe, J. Chem. Soc. **1934**, 1312.
[3] Mozingo and Adkins, J. Am. Chem. Soc. **60**, 669 (1938).

ETHYL DIACETYLACETATE

$$CH_3COCH_2CO_2C_2H_5 + CH_3COCl \xrightarrow{Mg} (CH_3CO)_2CHCO_2C_2H_5 + (H_2 + MgCl_2)$$

Submitted by A. SPASSOW.
Checked by NATHAN L. DRAKE, LEONARD SMITH, and JONATHAN W WILLIAMS.

1. Procedure

A MIXTURE of 12 g. (0.50 gram atom) of magnesium turnings, 130 g. (1.0 mole) of ethyl acetoacetate, 200 g. of benzene (dried over sodium), and 120 g. (1.50 moles) of acetyl chloride is heated under reflux for two hours in a 1-l. round-bottomed flask provided with a condenser closed by a calcium chloride tube and supported in an oil bath (85–90°) (Note 1). The yellow reaction mixture is cooled in an ice bath, and the liquid portion decanted into a separatory funnel. The residue in the flask is washed twice with 50-cc. portions of ether, and the ethereal solution poured over ice. The ether-water mixture is then added to the benzene solution in the separatory funnel, and the mixture is shaken thoroughly (Note 2); the aqueous layer is drawn off and discarded. The benzene-ether solution is washed once with 500 cc. of 5 per cent sodium bicarbonate solution, once with 50 cc. of water, and finally dried over calcium chloride. The ether and most of the benzene are removed by distillation from a water bath, and the remainder of the benzene is driven off at 50°/50 mm. The ethyl diacetylacetate is then precipitated from the residue as copper derivative by the addition of 1200 cc. of a saturated aqueous solution of copper acetate (Note 3). After addition of the copper acetate solution, the contents of the flask are shaken vigorously now and then and allowed to stand for an hour to ensure complete precipitation of the copper derivative. The blue copper derivative is filtered on a Büchner funnel, washed with two 50-cc. portions of water, and transferred directly to a separatory funnel where it is mixed with 600 cc. of ether.

Four hundred cubic centimeters of 25 per cent sulfuric acid is added, and the contents of the funnel are shaken continually until the copper derivative has disappeared (five to ten minutes). After separation of the ethereal layer, the aqueous layer is extracted twice with 100-cc. portions of ether, and the combined ethereal extracts are dried over calcium chloride. The ether is removed on the steam bath and the residual ester distilled under diminished pressure. A few drops come over up to 90°, but the bulk of the material distils at 92–98°/12 mm. Redistillation yields pure ethyl diacetylacetate boiling at 95–97°/12 mm. The yield is 80–90 g. (46–52 per cent of the theoretical amount).

2. Notes

1. Hydrogen and hydrogen chloride are evolved; this operation must be conducted in a hood.

2. The greater part of the magnesium remains unchanged. It should be removed by filtering the solution through a plug of *fine* glass wool in an ordinary funnel.

3. The saturated solution of copper acetate is prepared by dissolving 100 g. of finely pulverized copper acetate in 1200 cc. of boiling water. If the preparation contains basic salt, a few cubic centimeters of acetic acid is added, and the solution is filtered. The solution is cooled to 35° before use.

3. Methods of Preparation

Ethyl diacetylacetate has been prepared by Claisen from the sodium derivative of acetylacetone and ethyl chloroformate.[1] It has also been prepared from the sodium derivative of ethyl acetoacetate and acetyl chloride,[2,3,4] and from ethyl acetoacetate and acetyl chloride in the presence of magnesium.[5]

[1] Claisen, Ann. **277**, 171 (1893).
[2] James, ibid. **226**, 211 (1884).
[3] Elion, Rec. trav. chim. **3**, 250 (1884).
[4] Michael, Ber. **38**, 2088 (1905).
[5] Ogata, Nosaki, and Takagi, J. Pharm. Soc. Japan **59**, 105 (1939) [C. A. 33, 4230 (1939)].

ETHYL 1,16-HEXADECANEDICARBOXYLATE

(Octadecanedioic Acid, Diethyl Ester)

$$2C_2H_5O_2C(CH_2)_8CO_2K \xrightarrow{\text{electrolysis}} C_2H_5O_2C(CH_2)_{16}CO_2C_2H_5$$

Submitted by SHERLOCK SWANN, JR., RENÉ OEHLER, and P. S. PINKNEY.
Checked by LEE IRVIN SMITH, JAMES W. HORNER, JR., and J. W. CLEGG.

1. Procedure

To 86.5 g. (0.38 mole) of ethyl hydrogen sebacate (Org. Syn. 19, 45) is added slowly and with cooling 125–130 cc. of approximately 3 *N* potassium hydroxide. The solution is then diluted to approximately 250 cc., yielding a 1.5 *N* solution of potassium ethyl sebacate.

The solution of potassium ethyl sebacate (Note 1) is poured into a 500-cc. tall type beaker provided with a cooling coil (Note 2), a thermometer, a stirrer, a platinum sheet anode 45–55 sq. cm. in area (Note 3), and two platinum wire cathodes (Note 4). To the solution 10 g. of monoethyl sebacate (Note 5) is added.

The electrodes are connected to a suitable source of direct current, 10 amperes of which is allowed to pass through the cell. To the solution there is now added 40 g. more of monoethyl sebacate in portions of 10 g. each over a period of ten minutes (Note 6). The temperature of the cell is held below 50° by running cold water through the cooling coil (Note 7).

The run is finished in sixty to seventy minutes. The reaction will have reached completion when a few drops of the electrolyte removed with a pipet show an alkaline reaction to phenolphthalein. The alkalinity should be tested every ten minutes after the first forty-five.

When the electrolyte has become alkaline, the oily product floating on the top is removed by means of a pipet (Note 8). The oil is washed with an equal volume of 10 per cent potassium carbonate (Note 9), then with an equal volume of 3.5 per cent hydrochloric acid, and finally twice with half its volume of water (a little ether effectively breaks up any emulsions which may form at this point). It is then crystallized from methyl alcohol, filtered by suction, and washed twice while in the funnel with ice-cold methyl alcohol (Note 10). The product, snow-white and waxy in appearance, is dried in a desiccator over sulfuric acid. The yield is 16–22 g. (40–55 per cent of the theoretical amount) of material melting at 41–42°. These figures for the percentage yields, however, are based only upon the 50 g. of ethyl hydrogen sebacate used in the second part and no account is taken of the 86.5 g. used in preparing the electrolyte solutions. This preparation becomes practicable, therefore, only when several consecutive runs are made (Note 8).

2. Notes

1. The reaction mixture may require slight warming on the water bath to make a homogeneous solution.
2. The checkers used a copper cooling coil. This was slightly attacked during the electrolysis: the solution became blue, and copper deposited on the cathodes.
3. Convenient dimensions for the anode are 3.75 by 6.0 cm. (the area of the anode [both sides] used by the checkers was 52 sq. cm.). Care should be taken to submerge it in the solution to a depth such that the oil which gathers on the top of the solution during the electrolysis will not insulate it, thus increasing the current density. The wire tab of the platinum sheet may be sealed into a glass tube so that only the sheet is exposed to the solution.
4. The cathodes should be equidistant from the anode to ensure uniform current density on both sides of the anode.
5. As the potassium salt of monoethyl sebacate is decomposed during the electrolysis, the free acid forms new salt. The alkalinity of the solution may, therefore, be used as the end-point of the electrolysis.
6. If the 50 g. of monoethyl sebacate is added all at once, excessive foaming will occur.

7. Addition of more water (50 cc.) makes possible a much better control of the temperature.

8. If it is desired to prepare larger amounts of product, more free acid may be added to the solution without turning off the current after the product has been drawn off by the pipet. Between ten and fifteen 50-g. batches of monoethyl sebacate may be converted in this way. The length of time for a run will gradually increase with the number of runs. After ten to fifteen runs, the time required to convert a 50-g. batch is three and one-half to four hours. The electrolyte should then be renewed.

9. Unchanged mono ester may be recovered by acidification of the carbonate washings, followed by extraction with ether.

10. About the same amount of by-product as main product is in solution in the methyl alcohol. The first material which crystallizes is pure main product.

3. Methods of Preparation

Diethyl 1,16-hexadecanedicarboxylate has been prepared by the electrolysis of potassium ethyl sebacate.[1]

[1] Brown and Walker, Proc. Roy. Soc. Edin. **17**, 297 (1890); Trans. Roy. Soc. Edin. **36**, 222 (1890); Ann. **261**, 125 (1891); Fairweather, Proc. Roy. Soc. Edin. **45**, 283 (1925); Shiina, J. Soc. Chem. Ind., Japan **40**, Suppl. binding 324 (1937) [C. A. **32**, 499 (1938)].

ETHYL β-PHENYL-β-HYDROXYPROPIONATE

$$C_6H_5CHO + BrCH_2CO_2C_2H_5 + Zn \rightarrow C_6H_5\underset{}{\overset{OZnBr}{\overset{|}{C}}}HCH_2CO_2C_2H_5$$

$$C_6H_5\overset{OZnBr}{\overset{|}{C}}HCH_2CO_2C_2H_5 + H_2SO_4 \rightarrow C_6H_5CHOHCH_2CO_2C_2H_5 + ZnSO_4 + HBr$$

Submitted by Charles R. Hauser and David S. Breslow.
Checked by R. L. Shriner, W. M. Hoehn, and Vera A. Patterson.

1. Procedure

In a clean, dry, 500-cc., three-necked flask, fitted with a mechanical stirrer, a 250-cc. separatory funnel, and a reflux condenser (Note 1), the upper end of which is protected by a calcium chloride drying tube, is placed 40 g. (0.62 gram atom) of powdered zinc (Note 2).

A solution of 83.5 g. (0.50 mole) of ethyl bromoacetate (Note 3) and 65 g. (0.61 mole) of benzaldehyde (Note 4) in 80 cc. of dry benzene and 20 cc. of absolute ether is placed in the separatory funnel. About 10 cc. of this solution is added to the zinc, and the flask is warmed until the reaction starts (Note 5). The mixture is then stirred and the rest of the solution added at such a rate that the reaction mixture refluxes, care being taken that the reaction does not become too vigorous. The addition should take about an hour. The reaction mixture is refluxed for a half hour on a water bath after the addition of the solution is complete.

The flask is then cooled in an ice bath and the reaction mixture hydrolyzed by the addition of 200 cc. of cold 10 per cent sulfuric acid with vigorous stirring during the addition. The acid layer is drawn off and the benzene solution extracted twice with 50-cc. portions of 5 per cent sulfuric acid. The benzene solution is washed once with 25 cc. of 10 per cent sodium car-

bonate solution, then with 25 cc. of 5 per cent sulfuric acid (Note 6), and finally with two 25-cc. portions of water. The combined acid solutions are extracted with two 50-cc. portions of ether, and the combined ether and benzene solutions are dried with 5 g. of magnesium sulfate or Drierite. The solution is filtered, the solvent removed by distillation at atmospheric pressure from a steam bath, and the residue fractionated *in vacuo*. The ester is collected at 151–154°/11–12 mm. (128–132°/5–7 mm.). The total yield is 59–62 g. (61–64 per cent of the theoretical amount) (Note 7).

2. Notes

1. An efficient reflux condenser is necessary to prevent loss of solvent. The same precautions as to cleanliness of apparatus and absence of moisture should be observed in carrying out Reformatsky reactions as in reactions involving the Grignard reagent.

2. The zinc dust is purified by washing it rapidly with dilute sodium hydroxide solution, water, dilute acetic acid, water, alcohol, acetone, and ether. It is then dried in a vacuum oven at 100°.

3. Ethyl bromoacetate is a powerful lachrymator, and care should be exercised in handling it. A 10 per cent solution of ammonium hydroxide should be kept available to neutralize any of the bromo ester which may be spilled.

4. The benzaldehyde should be washed with two 50-cc. portions of 10 per cent sodium bicarbonate solution, dried, and distilled.

5. It is essential that the reaction start before any additional ethyl bromoacetate and benzaldehyde are added.

6. The acid extraction should be continued until no white precipitate of zinc hydroxide is formed on extraction with sodium carbonate. This step is important, since the zinc complex hydrolyzes much less readily than the corresponding magnesium complex. A small amount of unhydrolyzed complex forms at the interface of the benzene and acid solutions. It is most readily separated during the first alkaline extraction.

7. Ethyl α,α-dimethyl-β-phenyl-β-hydroxypropionate may be prepared in a similar manner. For instance, from 100 g. of ethyl α-bromoisobutyrate and 65 g. of benzaldehyde, 82.5 g. (73 per cent of the theoretical amount) of ethyl α,α-dimethyl-β-phenyl-β-hydroxypropionate, boiling at 153–158°/11 mm., is obtained. It may be recrystallized by dissolving it at 30° in 100 cc. of ligroin (30–60°), chilling the solution for several days, and decanting the clear liquid from the precipitate; m.p. 38.5–39°.

3. Methods of Preparation

Ethyl β-phenyl-β-hydroxypropionate has been prepared by esterification of β-phenyl-β-hydroxypropionic acid obtained by the addition of hydrogen bromide to cinnamic acid and subsequent hydrolysis.[1,2] The procedure given is based on that of Andrijewski [3] and of Blaise and Herman.[4]

HEMIN

$C_{34}H_{32}O_4N_4FeCl$

Submitted by HANS FISCHER.
Checked by C. R. NOLLER and G. A. SMITH.

1. Procedure

In a 5-l. round-bottomed flask equipped with a thermometer, reflux condenser, and dropping funnel are placed 4 l. of glacial acetic acid and 1 g. of sodium chloride. The acid is heated to boiling on a sand bath until the sodium chloride is in solution, and then 1 l. of defibrinated blood (Note 1) is added in a thin stream from the dropping funnel over a period of about thirty minutes. The blood should not touch the sides of the flask.

[1] Findlay and Hickmans, J. Chem. Soc. **1909**, 1004.
[2] Fittig and Binder, Ann. **195**, 131 (1877).
[3] Andrijewski, J. Russ. Phys. Chem. Soc. **40**, 1635 (1908).
[4] Blaise and Herman, Ann. chim. phys. [8] **23**, 532 (1911).

During this time the temperature is kept at 100–105°, and heating is continued for ten minutes after all the blood has been added. The flame is then removed and the mixture allowed to cool and stand overnight.

The precipitated hemin is removed by centrifuging (Note 2). If the centrifuging is carried out in 100-cc. tubes, each lot of tubes is centrifuged ten minutes, the supernatant liquid is decanted, more of the mixture added, and the centrifuging repeated. The hemin is allowed to accumulate in the tubes until all the mixture has been centrifuged, after which it is stirred with a glass rod and washed from the several tubes into one with 75 cc. of 50 per cent aqueous acetic acid. After centrifuging and decanting, the hemin is washed successively in the same manner with two 75-cc. portions of distilled water, one 50-cc. portion of 95 per cent alcohol, and one 50-cc. portion of ether. After the ether has been decanted the hemin is transferred to a watch glass by means of a rubber policeman and about 5 cc. of ether. After evaporation to dryness 3.5–4.5 g. of crude product is obtained.

For recrystallization, 5 g. of the crude hemin is placed in a 100-cc. Erlenmeyer flask, 25 cc. of pyridine is added, and the flask is shaken until the hemin has dissolved. Forty cubic centimeters of chloroform is added, and the flask is stoppered with a cork and shaken for fifteen minutes; the cork is carefully removed from time to time to release the pressure. The solution is then filtered with slight suction through a small Büchner funnel, and the Erlenmeyer flask and filter are washed with 15 cc. of chloroform.

During the shaking 350 cc. of glacial acetic acid is heated to boiling in a 600-cc. beaker under a hood, and 5 cc. of a saturated sodium chloride solution and 4 cc. of concentrated hydrochloric acid are added. The flame is extinguished, and the filtered hemin solution poured in a steady stream with stirring into the hot mixture; the suction flask is rinsed with 15 cc. of chloroform. After the mixture has stood for twelve hours, the crystals are filtered with suction on a small Büchner funnel and washed with 50 cc. of 50 per cent aqueous acetic acid, 100 cc. of distilled water, 25 cc. of alcohol, and 25 cc. of ether. Suction is continued

until the crystals are dry, when they can be readily removed. The recovery is 75–85 per cent.

2. Notes

1. Fresh blood obtained from a slaughter house is defibrinated by whipping it with a stiff vegetable-fiber brush followed by filtration with suction through a large Büchner funnel. The blood is stirred during the filtration to prevent settling of the erythrocytes. Beef blood was used for checking this preparation.

2. The hemin may be removed by filtration but it is usually so finely divided that centrifuging is easier and less loss results.

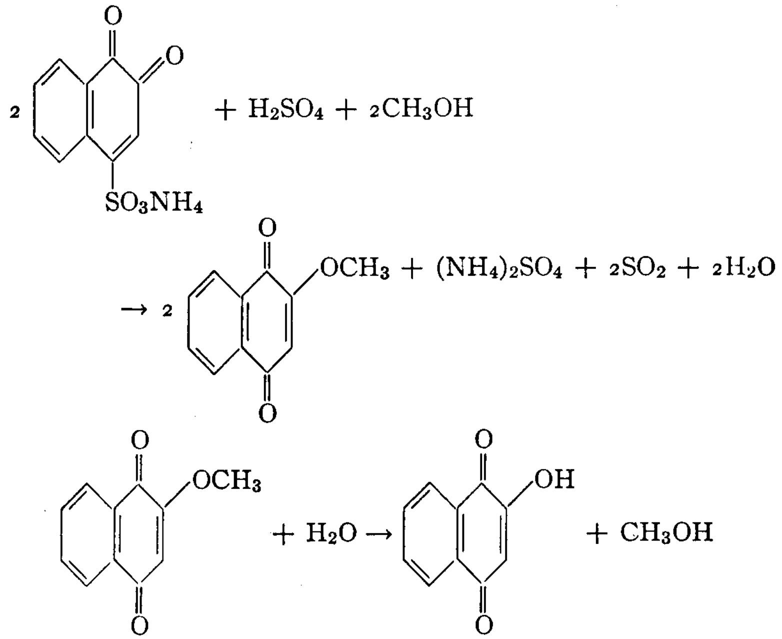
3. Methods of Preparation

Hemin has been synthesized,[1] but it is always prepared from blood.[2]

[1] Fischer and Zeile, Ann. **468**, 98 (1929).

[2] Nencki and Zaleski, Z. physiol. Chem. **30**, 390 (1900); Piloty, Ann. **377**, 358 (1910).

2-HYDROXY-1,4-NAPHTHOQUINONE



Submitted by L. F. Fieser and E. L. Martin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

One liter of absolute methyl alcohol is cooled in a 3-l., round-bottomed flask to 0° in an ice-salt bath, and 80 cc. of concentrated sulfuric acid is slowly added, with good shaking, the temperature being kept at 0°. The flask is removed from the freezing mixture, and 255 g. (1 mole) of ammonium 1,2-naphthoquinone-4-sulfonate (p. 91) is added and made into an even paste by thorough shaking. After standing for thirty minutes, during which time the temperature rises to 15–20°, the flask is heated gradually on the steam bath with continuous shaking and rotating so that the solution reaches its boiling point in about fifteen

minutes. The solution becomes red, sulfur dioxide is evolved, and methoxynaphthoquinone begins to separate. The mixture is kept boiling very gently, with continued shaking, for fifteen minutes, when the paste of separated material becomes very stiff. Two hundred and fifty cubic centimeters of methyl alcohol is added, and the heating and rotating continued for an additional fifteen to twenty minutes. The reaction mixture is cooled to 20–25°, water and ice are added until the flask is nearly filled, and the methoxynaphthoquinone is collected on a 15-cm. Büchner funnel and washed with cold water until the filtrate is nearly colorless; about 2–2.5 l. of water is required (Note 1).

The moist material is washed into a solution of 30 g. of sodium hydroxide in 1.5 l. of water, and the mixture is heated rapidly nearly to the boiling point. In about ten minutes all the ether is hydrolyzed, and a deep red solution results (Note 2). The hot solution is filtered by suction from a trace of residue, transferred to a 2-l. beaker, and acidified while still hot by adding 130 cc. of 6 *N* hydrochloric acid slowly, and with good stirring. The yellow suspension of hydroxynaphthoquinone thus obtained is cooled to 0° and allowed to stand for two hours (Note 3). The hydroxynaphthoquinone is collected, washed with 2 l. of cold water, dried overnight at room temperature, and finally to constant weight at 60–80°. The yield is 101–112 g. (58–65 per cent of the theoretical amount, based on ammonium 1,2-naphthoquinone-4-sulfonate; 99 per cent of the theoretical amount, based on methoxynaphthoquinone) (Note 4). The hydroxynaphthoquinone thus obtained is bright yellow in color, is granular, and melts, with decomposition, at about 188–189° (Note 5). It is of high quality, and for ordinary uses requires no further purification (Note 6).

2. Notes

1. The methoxynaphthoquinone weighs 111–122 g. (59–65 per cent of the theoretical amount). It melts at 181–182°, and can be further purified by crystallization from alcohol. The pure substance forms pale yellow needles, m.p. 183.5°.

2. Should the sodium salt separate during the heating or

filtration, it is brought into solution by adding about 1 l. of water and heating.

3. By allowing the precipitate to stand for the indicated period, the final product is granular, and the filtration is rapid.

4. Numerous modifications have been tried without improving the yield. The loss is probably due to a partial reduction of the quinone sulfonate by the sulfur dioxide liberated, but this was not prevented by adding manganese dioxide to the reaction mixture, and no pure product could be obtained from the mother liquor.

5. The temperature of decomposition varies with the rate of heating and with the nature of the glass capillary.

6. Crystallization from alcohol containing a trace of acetic acid gives glistening yellow needles, melting with decomposition at about 191–192°. The red samples of hydroxynaphthoquinone often mentioned in the literature are not completely pure. Such material, or crude material of any kind, is best purified through either the sodium salt or the methyl ether.

3. Methods of Preparation

Of the many reactions by which hydroxynaphthoquinone has been obtained,[1,2] only two have been developed into practical preparative methods, and both these utilize the inexpensive β-naphthol as the primary starting material. In the first method, this is converted into β-naphthoquinone (Org. Syn. **17**, 68), which reacts with acetic anhydride-sulfuric acid to give 1,2,4-trihydroxynaphthalene triacetate, which is then hydrolyzed and oxidized to the desired product. The yield of the acetylation reaction is about 75 per cent; that in the final step can be brought to 93 per cent of the theoretical amount by hydrolyzing with alcoholic alkali in an atmosphere of nitrogen and with a trace of sodium hydrosulfite present, then diluting with water, acidifying, and adding ferric chloride. The overall yield from β-naphthol can thus be brought to 54 per cent. The method is a good one, and it can be used to advantage for the preparation of many similar hydroxyquinones. With ordinary laboratory equipment, however, one is limited to 0.5-mole runs, and not more than about 50 g. of hydroxynaphthoquinone can be prepared at a time.

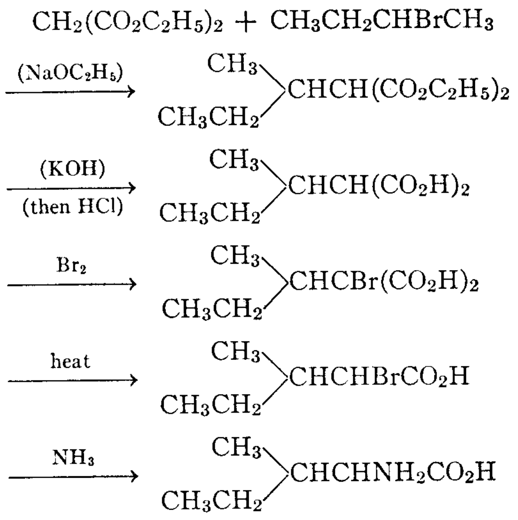
[1] Beilstein-Prager-Jacobson, VIII, 300 (1925).
[2] Thiele and Winter, Ann. **311**, 347 (1900).

The second method is that described above: β-naphthol is converted through the nitroso derivative and 1-amino-2-naphthol-4-sulfonic acid into naphthoquinone sulfonate, and this is subjected to acid hydrolysis. The sulfonate can be converted directly into hydroxynaphthoquinone by the action of concentrated sulfuric acid,[3,4] but the process is not so easily controlled as when the quinone is etherified as it is formed, and the ether subsequently hydrolyzed.[4] The overall yield from β-naphthol is 46 per cent of the theoretical amount, but all the reagents are inexpensive, and with ordinary apparatus, 150 g. of hydroxynaphthoquinone can be made conveniently in one run (from 300 g. of β-naphthol).

[3] Akt.-Ges. Anilinf., Ger. pat. 100,703 [Chem. Zentr. **70**, 766 (1899)].
[4] Fieser, J. Am. Chem. Soc. **48**, 2929 (1926).

dl-ISOLEUCINE

(α-Amino-β-methylvaleric Acid)



Submitted by C. S. MARVEL.*
Checked by W. E. BACHMANN and D. W. HOLMES.

1. Procedure

(*A*) *Diethyl sec.-Butylmalonate.*—To 700 cc. of absolute alcohol in a 2-l. three-necked, round-bottomed flask equipped with a long, wide-bore reflux condenser is added 35 g. (1.52 gram atoms) of sodium cut in pieces of suitable size. When all the sodium has reacted, the flask is placed on a steam cone and fitted with a mercury-sealed stirrer, a dropping funnel, and a reflux condenser bearing a calcium chloride tube (Note 1). The flask is heated, and 250 g. (1.56 moles) of diethyl malonate is added in a steady stream with stirring. After the ester addition, 210 g. (1.53 moles) of *sec.*-butyl bromide is added at such

* These directions are the result of the efforts of dozens of men who have worked on the preparation of isoleucine at the University of Illinois during the past twenty years.

a rate that the heat of reaction causes refluxing. The mixture is then stirred and refluxed for forty-eight hours. At the end of this time, the reflux condenser is exchanged for a downward condenser and the alcohol is distilled off (Note 2). The residue is treated with 200 cc. of water, shaken, and allowed to stand until the ester layer separates. The ester layer is separated from the aqueous layer and distilled from a 500-cc. two-necked flask fitted with a well-wrapped 18-in. Vigreux column. The fraction boiling at 110–120°/18–20 mm. is diethyl *sec.*-butylmalonate, and amounts to 274–278 g. (83–84 per cent of the theoretical amount).

(*B*) *α-Bromo-β-methylvaleric Acid.*—In a 2-l. three-necked, round-bottomed flask equipped with a stirrer and dropping funnel and placed on a steam cone, 250 g. of technical potassium hydroxide is dissolved in 200 cc. of water. To the hot solution, 250 g. (1.16 moles) of diethyl *sec.*-butylmalonate is added in a steady stream with vigorous stirring (Note 3). A tube connected to a vacuum line assists in the removal of alcohol. The mixture is stirred and heated for five hours (Note 4), and then the contents of the flask are transferred to a beaker fitted with a stirrer and surrounded by an ice bath. The cooling is hastened by the addition of 50 g. of ice, and when the temperature reaches 15°, technical hydrochloric acid is added at such a rate that the temperature does not rise above 20°. After the addition of about 250 cc. of acid, the monopotassium salt separates, necessitating stirring by hand until solution again occurs. When the solution is acid to Congo red (Note 5) it is transferred to a separatory funnel (Note 6).

The *sec.*-butylmalonic acid is extracted with three 200-cc. portions of ether, and the combined extracts are dried over calcium chloride overnight. The ether solution is then decanted into a 2-l. three-necked flask fitted with a mercury-sealed stirrer, reflux condenser, and dropping funnel. Five cubic centimeters of bromine is added at one time and the solution stirred until decolorized (Note 7). Then 50 cc. more bromine is added dropwise at such a rate that the ether refluxes gently. When all the bromine has been added, 200 cc. of water is added through

the dropping funnel dropwise so as to produce no foaming or violent reaction.

The ether layer containing the bromomalonic acid is separated from the aqueous layer and the ether removed by distillation from a steam cone. The residual liquid is decarboxylated by refluxing for five hours in a 500-cc. round-bottomed flask on an oil bath heated to 130°. The bromo acid is then separated from the small amount of water and distilled. The material distilling at 125–140°/18–20 mm. is α-bromo-β-methylvaleric acid (Note 8). The yield is 150.5 g. (66.7 per cent of the theoretical amount).

(*C*) *dl-Isoleucine.*—One hundred and fifty grams (0.77 mole) of α-bromo-β-methylvaleric acid is added to 645 cc. of technical ammonium hydroxide (sp. gr. 0.90) in a 1.5-l. round-bottomed flask. A stopper is wired in and the flask allowed to stand at room temperature for a week (Note 9). The stopper is removed and the mixture heated on a steam cone overnight to remove ammonia. The aqueous solution is concentrated under reduced pressure until bumping becomes violent (about 300 cc.). The mixture is then cooled to 15° and the crystals collected on a filter. The crystals are washed with 40 cc. of alcohol and dried. The filtrate is again concentrated to about 150 cc. and a second crop of crystals obtained. This second crop is washed with 25 cc. of water and then with 25 cc. of 95 per cent alcohol. The yield of crude product is 65 g.

The isoleucine is recrystallized by dissolving it in 850 cc. of water heated to 95° on a steam cone. The solution is decolorized by treatment with a gram of Norite for thirty minutes and is then filtered hot. To the hot solution is added 425 cc. of 95 per cent alcohol, and the flask is placed in an icechest overnight. The yield of pure product is 38 g. An additional crop of 12 g. may be obtained by concentrating the mother liquors from the recrystallization to about 100 cc. and adding an equal volume of alcohol. This second crop is washed with 10 cc. of cold water and 10 cc. of cold alcohol. The total yield is 50 g. (49 per cent of the theoretical amount). The product decomposes at 278–280° in a sealed evacuated capillary (Note 10).

2. Notes

1. The submitters carried out the preparation on a run ten times this size, using a 12-l. round-bottomed flask. After the sodium had reacted, the flask was fitted with a stopper containing the stirrer and two angle tubes connected respectively to a reflux condenser and a dropping funnel. The time allowed for the various reactions to take place was the same as for the smaller run. The percentage yields of the various products were practically identical.

2. On a run ten times this size, the submitters distilled the alcohol into another 12-l. flask connected by means of an adapter and fitted with the wide-bore reflux condenser originally used. The sodium necessary for a second run was added to the second flask as the alcohol distilled into it; on the large run this took four to six hours.

3. The ester is added quite slowly at first, until the reaction gets under way, and then more rapidly.

4. Water is added if necessary to keep the mass from solidifying.

5. About 400 cc. of acid is required.

6. For a run ten times this size, the solution is transferred to a 12-l. round-bottomed flask fitted with a stopper containing a large stopcock which barely pierces the stopper and a glass tube which reaches to the bottom of the flask. A flask so fitted can be used as a large separatory funnel. The stopper is wired when the flask is upturned.

7. It is important that the first 5-cc. portion react completely; otherwise the bromination will not go smoothly and the solution may foam out of the condenser.

8. If the decarboxylation was not complete it will be finished here. Occasionally it is some time before a good water pump will maintain constant pressure.

9. On a larger run, the submitters allowed 350 g. of the bromoacid and 1500 cc. of ammonium hydroxide in a 3-l. flask to stand for a week. The contents of four such flasks, including

any solid material, were combined in a 12-l. round-bottomed flask and heated on a steam cone overnight.

10. The product obtained in this manner has the calculated amount of amino nitrogen.

3. Methods of Preparation

dl-Isoleucine has been prepared by the reduction and subsequent hydrolysis of ethyl α-oximino-β-methyl-*n*-valerate;[1] by the action of aqueous ammonia on α-bromo-β-methyl-*n*-valeric acid;[2] and from ethyl *sec.*-butylbromomalonate by saponification, decarboxylation, and amination.[3] The procedure described above is a combination of these last two methods.

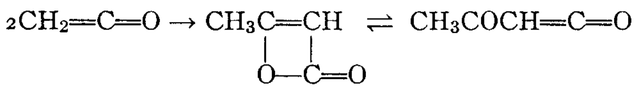
[1] Bouveault and Locquin, Compt. rend. **141**, 115 (1905); Bull. soc. chim. (3), **35**, 965 (1906).

[2] Ehrlich, Ber. **41**, 1453 (1908); Brasch and Friedmann, Beitr. Chem. Physiol. Path. (2) 376 (1908).

[3] Romburgh, Rec. trav. chim. **6**, 150 (1887).

KETENE DIMER

(Acetylketene; "Diketene")



Submitted by Jonathan W. Williams and John A. Krynitsky.
Checked by Nathan L. Drake and Joseph Lann.

1. Procedure

Three 300-cc. gas-washing cylinders (Note 1) are connected in series, and the second and third cylinders are charged with 150 cc. each of dry acetone. Each of the three cylinders is immersed, in a thermos bottle, in sufficient Dry Ice-acetone cooling mixture to cover half of the cylinder. Ketene gas, prepared by the pyrolysis of acetone (Note 2), is passed through the system (Note 3) until a quantity of 2 moles has been introduced. This

process requires four to four and one-half hours. During this time, after the ketene has been passing through the system for one and one-half hours, the Dry Ice-acetone cooling mixture is removed from the thermos bottle around the first cylinder. The cold thermos bottle is then replaced around the cylinder. Two hours after the completion of the ketene passage, the cooling mixture is removed from the second thermos bottle, and six hours later the third thermos bottle is emptied, both bottles being immediately restored to position. The entire system should be at room temperature twenty-four hours after the beginning of the run.

The liquids from all three cylinders are combined and fractionally distilled (Note 4). Most of the acetone is removed at room temperature under a pressure of 20 mm.; the last small portion is removed under atmospheric pressure. When the distillation temperature reaches 120°, the system is evacuated to a pressure of 80–100 mm. (Note 5), and the ketene dimer is collected within the boiling range 67–69°/92 mm. The yield of pure product is 42–46 g. (50–55 per cent of the theoretical amount) (Notes 6 and 7).

2. Notes

1. The gas-washing cylinders are preferably without flanges. Those used by the submitters were prepared from 45-mm. Pyrex tubing, measured 28 cm. in length, and were fitted with 29/42 standard taper ground-glass joints. The inlet tubes extended two-thirds of the way into the cylinders.

2. Ketene may be generated conveniently from acetone by means of a "ketene lamp."[1] This apparatus was used by submitters and checkers. Other apparatus (Org. Syn. Coll. Vol. **1**, 324) might also be used.

3. The effluent gases from the third cylinder should be conducted to an efficient hood, or passed through a washing bottle containing a 10 per cent aqueous solution of sodium hydroxide.

[1] Williams and Hurd, J. Org. Chem. **5**, 122 (1940).

4. The submitters and checkers used a column of the Whitmore–Lux type (p. 14, Note 3).

5. Pressure between these limits is the optimum for this distillation. At higher pressure too much polymerization to dehydroacetic acid occurs, and at a lower pressure special cooling methods are necessary to prevent loss of distillate by evaporation.

6. A viscous dark red residue remains in the distillation flask. This material is mostly dehydroacetic acid.

7. The ketene dimer may be kept in a tightly stoppered bottle in the dark without appreciable further polymerization for about a week.[2c]

3. Method of Preparation

The procedure described is a modification of the method of Chick and Wilsmore,[3] which has been studied by several other workers.[2]

[2] (*a*) Hurd, Sweet, and Thomas, J. Am. Chem. Soc. **55**, 335 (1933). (*b*) Hurd and Williams, ibid. **58**, 962 (1936). (*c*) Boese, Ind. Eng. Chem. **32**, 16 (1940).

[3] Chick and Wilsmore, J. Chem. Soc. **1908**, 946; **1910**, 1978.

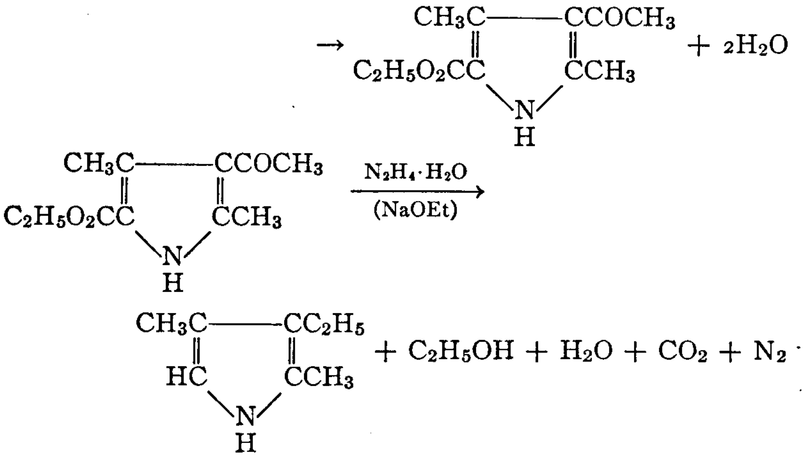
KRYPTOPYRROLE

(2,4-Dimethyl-3-ethylpyrrole)

$$CH_3COCH_2CO_2C_2H_5 + HNO_2 \rightarrow CH_3COC(NOH)CO_2C_2H_5 + H_2O$$

$$CH_3COC(NOH)CO_2C_2H_5 + 4(H) \xrightarrow{(Zn + CH_3CO_2H)} CH_3COCH(NH_2)CO_2C_2H_5 + H_2O$$

$$CH_3COCH(NH_2)CO_2C_2H_5 + CH_3COCH_2COCH_3$$



Submitted by Hans Fischer.
Checked by Homer Adkins and Ivan A. Wolff.

1. Procedure

In a 3-l. three-necked flask provided with a stirrer and surrounded by an ice bath are placed 402 g. (3.09 moles) of ethyl acetoacetate (Note 1) and 1200 cc. of glacial acetic acid. To this solution is then added dropwise with stirring a solution of 246 g. (3.55 moles) of sodium nitrite in 400 cc. of water. The rate of addition is controlled so that the temperature does not rise above 12°. After the sodium nitrite solution has been added,

the mixture is stirred an additional two to three hours. It is then allowed to warm up to room temperature and stand about twelve hours, after which 348 g. (3.48 moles) of acetylacetone (Org. Syn. **20**, 6) is added at one time.

To the reaction mixture 450 g. of zinc dust (Note 2) is added in portions of about 10 g. with vigorous stirring. The rate of addition is regulated so that the temperature never rises above 60°. After the addition is complete (Note 3), the mixture is refluxed for two to three hours on a hot plate until the unreacted zinc dust collects in balls. The hot solution is then poured through a fine copper sieve, with stirring, into 30 l. of ice water. The crude product which separates is contaminated with zinc (Note 4). On recrystallization from 1500 cc. of 95 per cent ethyl alcohol, 360–390 g. of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole (m.p. 143–144°) is obtained (55–60 per cent of the theoretical amount based on the ethyl acetoacetate used) (Note 5). A second recrystallization may be necessary to secure a perfectly white product, but the product of the first recrystallization is sufficiently pure for conversion to kryptopyrrole.

Thirty grams of sodium is dissolved in 430 cc. of absolute alcohol, the last portions by heating under reflux. The hot alcoholic solution is poured into an autoclave (Note 6), 75 g. (0.36 mole) of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole stirred in, and 36 cc. of hydrazine hydrate (Note 7) added. The autoclave is then heated and the mixture kept at 165–170° for twelve hours. After cooling, the contents of the autoclave are emptied into a 2-l. round-bottomed flask. The autoclave is rinsed with a small amount of absolute alcohol and these washings are added to the 2-l. flask. Then 50 cc. of water is added, and the alcohol is distilled from a steam bath, followed by steam distillation of the kryptopyrrole. The alcoholic distillate is collected separately. A glass condenser should be used for the steam distillation, as in some runs a white solid which melts around room temperature begins to appear after about 1 l. has distilled. The condenser water is turned off periodically to allow the solid in the condenser to melt. Steam distillation is continued until the drops of distillate are no longer cloudy, that is, after about

1700 cc. has distilled. A slow stream of nitrogen is passed over the surface of the distillate during the steam distillation (Note 8).

The alcoholic distillate is diluted to 2 l. with distilled water, and extracted with a 500-cc. and then a 300-cc. portion of ether. The steam distillate is extracted twice with this ether extract, and twice more with 250-cc. portions of fresh ether. The ether extracts are combined and dried with 150 g. of anhydrous sodium sulfate. The space above the solution is filled with nitrogen. The ether solution is decanted, and the sodium sulfate washed three times with distilled ether. The ether is then distilled, the temperature of the bath about the flask being raised finally to 130°. The kryptopyrrole is then fractionated under reduced pressure (Note 9). The yield of water-white product boiling within a 1.5° range (85.5–87°/12.5 mm.; 92.5–94°/18 mm.) is 22–25.5 g. (50–58 per cent of the theoretical amount).

2. Notes

1. The ester used was a commercial product and was not further purified.

2. The zinc dust should be at least 80 per cent pure.

3. Before refluxing the reaction mixture, enough time should be allowed for the zinc dust to react completely; otherwise considerable trouble with foaming may be encountered.

4. The crude pyrrole darkens on exposure to light, especially when exposed to direct sunlight. The recrystallized product is unaffected by light.

5. The preparation can be carried out in larger or smaller quantities with proportionate amounts of materials and volumes of containers without affecting the yield. The amounts specified here are 60 per cent of those used by the submitter.

6. The checkers used a steel hydrogenation bomb with a void of 650 cc. from which the inside bent steel tube leading to the gauge assembly was removed. A steel plug was inserted in the opening which usually carries a gauge. The temperature was controlled by an automatic regulator, and the reaction mixture was not shaken or stirred.

7. Hydrazine hydrate may be prepared by the ammonolysis of hydrazine sulfate,[1] followed by the addition of water.

Liquid ammonia is placed in a 1-pint thermos bottle, and 60 g. of Eastman's hydrazine sulfate is added in small portions while the liquid is stirred mechanically. After the addition is complete, stirring is continued for thirty minutes. The mixture is filtered into another thermos bottle through a fluted filter paper, and the remaining solid washed twice with liquid ammonia by transferring it back to the original flask, stirring, and again filtering. On evaporation of the liquid ammonia 7.5–10 g. of colorless liquid is left, 51–68 per cent of the theoretical yield, calculated as anhydrous hydrazine. Five cubic centimeters of water is then added. Three to four such runs are required to obtain the hydrazine hydrate needed in this preparation.

8. Kryptopyrrole is very sensitive to oxidation and should be handled with a minimum amount of exposure to the air. It is best stored in sealed glass tubes. If a capillary ebullition tube is used during distillation under reduced pressure, the tube should be connected to a supply of nitrogen.

9. A Vigreux, a modified Widmer, or other column may be used for this separation.

3. Methods of Preparation

Kryptopyrrole has been obtained by the degradation of bilirubin, hemin, rhodoporphyrin, etc.[2] The synthesis given above is based upon the work of Knorr and Hess.[3]

[1] Browne and Welsh, J. Am. Chem. Soc. **33**, 1728 (1911).

[2] Fischer-Orth, "Die Chemie des Pyrrols," p. 53, Akademische Verlagsgesellschaft, Leipzig, 1934.

[3] Knorr and Hess, Ber. **44**, 2765 (1911).

LACTAMIDE

$$CH_3CH(OH)CO_2C_2H_5 + NH_3 \rightarrow CH_3CH(OH)CONH_2 + C_2H_5OH$$

Submitted by J. Kleinberg and L. F. Audrieth.
Checked by Homer Adkins and William H. Bateman.

1. Procedure

One hundred and twenty-five grams (1.06 moles) of ethyl lactate is placed in a suitable Pyrex container which is subsequently cooled in a solid carbon dioxide-acetone bath. When the ester has been cooled below the boiling point of ammonia (Note 1), 125 cc. of liquid ammonia (Note 2) is added. The mixture is then placed in a specially constructed steel pressure apparatus (Note 3) and permitted to come to room temperature. After twenty-four hours (Note 4) the excess of ammonia is allowed to escape slowly through the gas outlet of the bomb. The last traces of ammonia are removed under reduced pressure. The reaction product is stirred with 200 cc. of absolute ether to dissolve unchanged ester and alcohol. The residue is filtered, washed with ether, and air-dried. The yield of lactamide melting at 74–75° amounts to 65–70 g. (70–74 per cent of the theoretical amount) (Note 5).

2. Notes

1. Care must be taken to cool the ester below the boiling point of ammonia before addition of the ammonia, to avoid loss of ester by spattering.

2. For manipulative procedures employing liquid ammonia see Franklin, "The Nitrogen System of Compounds," A.C.S. Monograph 68, Appendix, Reinhold Publishing Corporation, New York, 1935; also, Fernelius and Johnson, J. Chem. Education **6**, 441 (1929).

3. The steel bomb in which the reaction is carried out is depicted in Fig. 2. It consists of a cylindrical tube (A) of

ordinary steel to which a steel bottom (B) has been welded. A 1-in. flange (C) is welded to the top of the container extending about 3/16 in. above the top of the bomb. The lead gasket (D) is pressed into the groove (E) when the cover of stainless steel is tightened by means of six steel bolts (G). The top (F) is

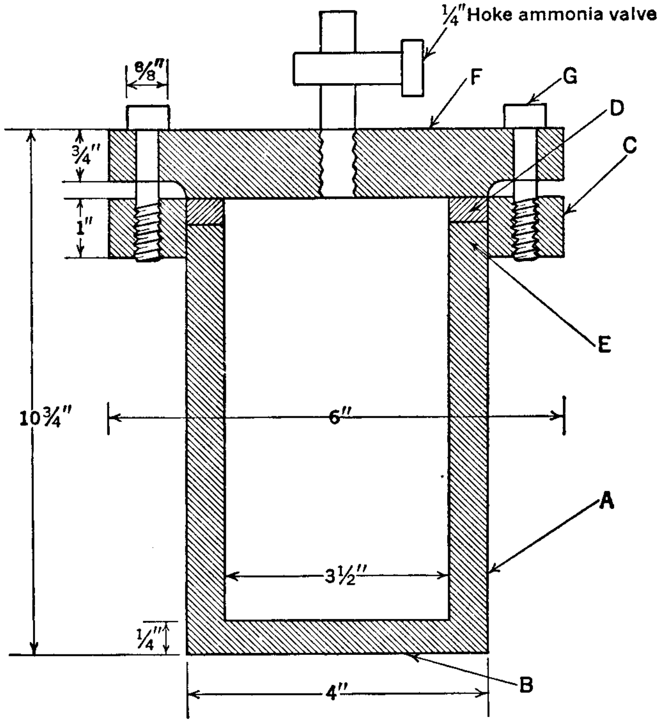


FIG. 2

machined to make a tight seal on the gasket (D). A ¼-in. steel Hoke ammonia valve serves as the gas outlet. The cross-sectional dimensions are noted in the diagram. The checkers carried out the reaction in a glass beaker which was set in a steel reaction vessel such as is used for hydrogenations at pressures of 50–500 atm.[1]

[1] Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," p. 31, University of Wisconsin Press, Madison, Wisconsin, 1937; Ind. Eng. Chem. Anal. Ed. **4**, 342 (1932).

4. Increase in reaction time causes no appreciable increase in yield of amide.

5. This method has been used for the preparation of numerous amides.[2] However, with many esters it is necessary to heat the reaction mixture to 200–250° for a few hours. Ethyl mandelate is like ethyl lactate in that it gives a good yield (75–80 per cent of the theoretical amount) of mandelamide at room temperatures.

3. Methods of Preparation

Lactamide has been prepared by the action of gaseous ammonia on ethyl lactate [3] and from lactic anhydride [4] and gaseous ammonia. It has been made also by the action of ammonia gas on lactide.[5] The amide was obtained in excellent yields by treatment of the acetone condensation product of lactic acid with ammonia.[6] Amides have been prepared by the reaction of liquid ammonia with esters at temperatures varying from −33° to 250°.[7,8,2]

[2] Wojcik and Adkins, J. Am. Chem. Soc. **56**, 2421 (1934), Paden and Adkins, ibid. **58**, 2497 (1936).

[3] Brüning, Ann. **104**, 197 (1857).

[4] Wurtz and Friedel, Ann. chim. phys. (3) **63**, 108 (1861).

[5] Wislicenus, Ann. **133**, 259 (1865).

[6] Oeda, Bull. Chem. Soc. Japan **11**, 385 (1936).

[7] Glattfeld and MacMillan, J. Am. Chem. Soc. **58**, 898 (1936).

[8] Audrieth and Kleinberg, J. Org. Chem. **3**, 312 (1938).

dl-LEUCINE

(Isocaproic Acid, α-amino)

$$(CH_3)_2CHCH_2CH_2CO_2H + Br_2 \xrightarrow{(PCl_3)} (CH_3)_2CHCH_2CHBrCO_2H + HBr$$

$$(CH_3)_2CHCH_2CHBrCO_2H + 2NH_3 \longrightarrow (CH_3)_2CHCH_2CHNH_2CO_2H + NH_4Br$$

Submitted by C. S. MARVEL.*
Checked by HOMER ADKINS and ROBERT GANDER.

1. Procedure

(A) *α-Bromoisocaproic Acid.*—Five hundred grams (4.3 moles) of commercial isocaproic acid is mixed with 250 cc. of benzene in a 2-l. round-bottomed flask, and the water and benzene are removed by distillation through a short column until the temperature of the vapors reaches 100°. The temperature rises rapidly as soon as the last of the benzene is removed. The residual acid is cooled to room temperature, 743 g. (4.65 moles, 243 cc.) of dry bromine (Note 1) is added, and the flask is fitted with a long condenser and placed in an oil bath. The top of the condenser is connected to an empty 500-cc. Erlenmeyer flask which acts as a safety flask, and this in turn leads to a gas-absorption trap (Note 2). Ten cubic centimeters of phosphorus trichloride is added to the mixture through the top of the condenser, and the flask is heated to 80–85°. The bromination proceeds smoothly at this temperature and is allowed to continue for eight to fifteen hours until the dark red color of bromine disappears from the condenser. When it has, the temperature is raised to 100–105° and kept there two hours. The contents of the flask are transferred to a 1-l. modified Claisen flask or a flask attached to a Widmer column and distilled. The fraction boiling at 125–131°/12 mm. is collected. The yield amounts to 530–550 g. (63–66 per cent of the theoretical amount). The low boiling fraction is mainly isocaproic acid (Note 3).

* These directions are the results of the efforts of dozens of men who have worked on the preparation of leucine at the University of Illinois during the past twenty years.

(B) *dl-Leucine.*—To 1500 cc. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask is added 300 g. (1.56 moles) of α-bromoisocaproic acid. A rubber stopper is wired in, and the flask is allowed to stand for a week at room temperature. The crude leucine from four such flasks is collected on a filter and washed with 400 cc. of alcohol. This crop amounts to about 300 g. The ammonia is removed from the filtrate by heating the solution in a 12-l. flask on a steam cone overnight. The solution is concentrated under reduced pressure until vigorous bumping occurs (about 2.5 l.). The mixture is then cooled to about 15° and filtered. The precipitate is washed with 250 cc. of cold water and 250 cc. of 95 per cent alcohol. The total yield of crude leucine in the two fractions is 440–460 g.

The amino acid is recrystallized by dissolving all the crude material in 12.5 l. of water heated to 95° on a steam cone. The hot solution is treated with 20 g. of Norite for thirty minutes and filtered hot. An equal volume of 95 per cent alcohol is added immediately, and the flask is placed in the icechest overnight. The crystalline material is collected on a filter and washed with 200 cc. of 95 per cent alcohol. The yield of pure leucine in this fraction is 290–300 g. An additional crop is obtained by evaporating the mother liquors under reduced pressure until considerable solid separates (liquid volume about 1 l.), adding an equal volume of alcohol, and cooling. This crop is washed with 100 cc. of cold water and then with 200 cc. of alcohol; it amounts to 60–65 g. The total yield of pure leucine is 350–365 g. (43–45 per cent of the theoretical amount). It decomposes at 290–292° (uncorr.) in a sealed capillary (Note 4).

2. Notes

1. The bromine is dried by shaking with 500 cc. of C.P. concentrated sulfuric acid.

2. The hydrogen bromide may be collected in water and

distilled to give constant-boiling hydrobromic acid. See Org. Syn. Coll. Vol. 1, 23.

3. The low-boiling fractions (105–115 g.) may be combined with the next portion of acid to be brominated, or several such fractions may be collected and brominated together. If this last is done only two-thirds as much bromine is used as in the original run.

4. The amino nitrogen content of leucine prepared in this way checks with the theoretical value.

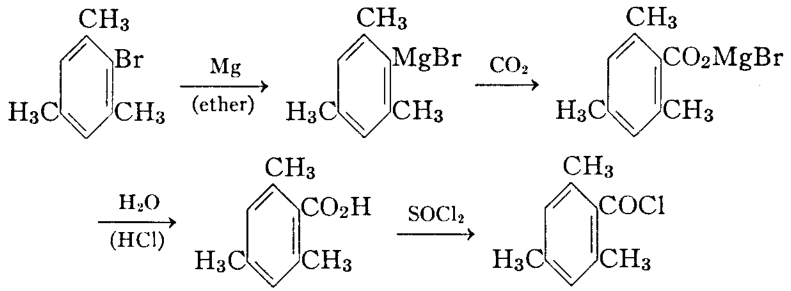
3. Methods of Preparation

dl-Leucine has been prepared by the hydrolysis of isobutylhydantoin with barium hydroxide;[1] by reduction and hydrolysis of α-oximinoisocaproate;[2] by racemization of *l*-leucine;[3] by the action of ammonia and hydrogen cyanide on isovaleraldehyde followed by hydrolysis;[4] by the action of heat on isobutylmalonylazidic acid followed by hydrolysis;[5] by the action of ammonia on α-bromoisocaproic acid;[6] by the condensation of isobutyl halides and sodio aminomalonic ester[7] or sodio benzoylaminomalonic ester[8] followed by hydrolysis; by the condensation of isobutyraldehyde and hippuric acid followed by reduction and hydrolysis.[9] The method described above is essentially the Fischer method[6] and is undoubtedly the best and cheapest procedure for the synthesis of large amounts of this amino acid.

[1] Pinner and Spilker, Ber. **22**, 696 (1889).
[2] Bouveault and Locquin, Bull. soc. chim. (3) **31**, 1181 (1904).
[3] Schulze and Bosshard, Ber. **18**, 389 (1885); Z. physiol. Chem. **10**, 135 (1886); Fischer, Ber. **33**, 2372 (1900).
[4] Limpricht, Ann. **94**, 243 (1855); Hüfner, J. prakt. Chem. (2) **1**, 10 (1870); Schulze and Likiernik, Z. physiol. Chem. **17**, 516 (1893); Abderhalden and Wybert, Ber. **49**, 2455 (1916).
[5] Curtius, J. prakt. Chem. (2) **125**, 211 (1930).
[6] Fischer, Ber. **37**, 2486 (1904).
[7] Locquin and Cherchez, Compt. rend. **186**, 1360 (1928).
[8] Redemann-Schmidt, "Chemistry of the Amino Acids and Proteins," p. 50, Thomas, Baltimore, Md., 1938.
[9] Erlenmeyer and Kunlin, Ann. **316**, 145 (1901).

MESITOYL CHLORIDE

(β-Isodurylyl Chloride)



Submitted by R. P. Barnes.
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

In a 2-l. three-necked flask, fitted with a condenser protected by a drying tube, a dropping funnel, and a sealed stirrer, are placed 24.3 g. (1 gram atom) of magnesium turnings, a small crystal of iodine, enough absolute ether to cover the magnesium, and 10 g. (0.05 mole) of bromomesitylene (Org. Syn. 11, 24). The bottom of the flask is warmed with the hand or a warm cloth until the reaction begins. The mixture is then stirred gently during the gradual addition of 190 g. (0.95 mole) of bromomesitylene dissolved in 500 g. (700 cc.) of absolute ether. When all the ethereal solution has been added, the reaction mixture is refluxed for about two hours, or until all the magnesium has dissolved. A large excess of solid carbon dioxide is now added slowly in small pieces with rapid stirring (Note 1). The resulting tough addition product is decomposed by pouring, with stirring, into a large volume of finely crushed ice to which has been added 100 cc. (1.2 moles) of concentrated hydrochloric acid. The ether is removed by evaporation and the resulting oily solid filtered, dissolved in 200-400 cc. of hot methyl alcohol, filtered, and thrown out by dilution with 1 l. of ice-water. The

crude mesitoic acid melts between 135° and 148° and weighs 110–120 g. The acid is recrystallized from petroleum ether (b. p. 90–100°), about 10 cc. of petroleum ether being used per gram of the crude acid. The product, melting at 150–152° after one recrystallization, weighs 90–100 g. (55–61 per cent of the theoretical amount) (Note 2).

A mixture of 90 g. (0.55 mole) of mesitoic acid and 100 g. (63 cc., 0.84 mole) of thionyl chloride in a 500-cc. large-mouthed Claisen flask, with the side arm and adjacent neck closed, and with the other neck fitted with a condenser protected by a drying tube, is refluxed gently until the evolution of sulfur dioxide and hydrogen chloride ceases (Note 3). The excess thionyl chloride is removed by distillation at atmospheric pressure, and the residual acid chloride is distilled at 143–146°/60 mm. (Note 4). The yield is 90–97 g. (90–97 per cent of the theoretical amount).

2. Notes

1. The Grignard reagent may be carbonated by pouring it slowly over Dry Ice contained in a 2-l. beaker. The yield is unchanged.

2. A small amount of mesitoic acid can be recovered by concentrating the filtrate to a small volume and cooling it.

3. This requires from one to two hours. The reaction mixture may also be allowed to stand overnight at room temperature, in which case no heating is necessary.

4. The boiling point varies with the rate of distillation.

3. Methods of Preparation

Mesitoic acid has been obtained by hydrolysis of its amide which was prepared from mesitylene, carbamyl chloride, and aluminum chloride in carbon disulfide.[1] It has been prepared by heating isodurene with dilute nitric acid,[2,3] in small yields by the distillation of 2,4,6,-trimethylmandelic acid,[4] by dry distillation of 2,4,6-trimethylphenylglyoxylic acid,[4,5] by oxidation of 2,4,6-trimethylphenylglyoxylic acid with potassium permanganate,[6] and by treating 2,4,6-trimethylphenylglyoxylic acid with concentrated sulfuric acid either with heating[7] or in the cold.[8] The preparation of the acid from 2,4,6-trimethylphenylmagnesium bromide and a stream of carbon dioxide has been described.[9]

The method for the preparation of the chloride is the general method for preparing aromatic acid chlorides with thionyl chloride,[10] which has been applied to the preparation of mesitoyl chloride.[9]

[1] Michael and Oechslin, Ber. **42**, 317 (1909).
[2] Jannasch and Weiler, ibid. **27**, 3441 (1894).
[3] Jacobsen, ibid. **15**, 1853 (1882).
[4] Meyer and Molz, ibid. **30**, 1270 (1897).

ω-METHOXYACETOPHENONE

$$C_6H_5MgBr + CH_3OCH_2CN \rightarrow CH_3OCH_2C({=}NMgBr)C_6H_5$$

$$2CH_3OC({=}NMgBr)C_6H_5 + H_2O + 2H_2SO_4 \rightarrow 2CH_3OCH_2COC_6H_5 + (NH_4)_2SO_4 + MgSO_4 + MgBr_2$$

Submitted by R. B. Moffett and R. L. Shriner.
Checked by W. E. Bachmann and W. S. Struve.

1. Procedure

A SOLUTION of phenylmagnesium bromide is prepared in a 2-l. three-necked flask, fitted with a separatory funnel, reflux condenser, and a mercury-sealed stirrer, from 8.8 g. (0.36 gram atom) of magnesium, 56.5 g. (38 cc., 0.36 mole) of bromobenzene, and a total of 350 cc. of dry ether by the procedure described in Org. Syn. Coll. Vol. 1, 221.

To the solution of the Grignard reagent, cooled by an ice-salt bath, a mixture of 21.3 g. (0.3 mole) of methoxyacetonitrile (Org. Syn. **13**, 56) and 50 cc. of dry ether is slowly added with

[5] Feith, Ber. **24**, 3542 (1891).
[6] Claus, J. prakt. Chem. (2) **41**, 506 (1890).
[7] van Scherpenzeel, Rec. trav. chim. **19**, 377 (1900).
[8] Hoogewerff and van Dorp, ibid. **21**, 349 (1902).
[9] Kohler and Baltzly, J. Am. Chem. Soc. **54**, 4015 (1932).
[10] Meyer, Monatsh. **22**, 415 (1901).

stirring. The colorless addition product separates at once. After standing at room temperature for two hours, the mixture is again cooled and then decomposed by adding, with stirring, 500 cc. of water and cracked ice, and then 100 cc. of cold dilute sulfuric acid (Note 1). When the decomposition is complete (Note 2), the ether layer is separated and the aqueous layer is extracted with a little ether. This ether extract is combined with the ether layer, and the whole is washed with 5 per cent aqueous sodium carbonate solution and then with water. The solution is dried with anhydrous sodium sulfate.

The ether is removed by distillation from a steam bath, and the residue is distilled under diminished pressure. ω-Methoxyacetophenone is a colorless liquid which boils at 118–120°/15 mm. or 228–230°/760 mm. (Note 3). The yield is 32–35 g. (71–78 per cent of the theoretical amount, based on the methoxyacetonitrile).

2. Notes

1. One volume of concentrated sulfuric acid is added to two volumes of water, and the mixture is cooled in an ice-salt bath.

2. The two layers should be light yellow in color with only a small amount of solid or tarry material present.

3. The checkers observed a boiling point of 110–112°/9 mm.

3. Method of Preparation

The method described is essentially that of Pratt and Robinson.[1]

[1] Pratt and Robinson, J. Chem. Soc. **1923**, 748.

METHYL ISOTHIOCYANATE

$$CH_3NH_2 + CS_2 + NaOH \rightarrow CH_3NHCS_2Na + H_2O$$
$$CH_3NHCS_2Na + ClCO_2C_2H_5 \rightarrow CH_3NHCS_2CO_2C_2H_5 + NaCl$$
$$CH_3NHCS_2CO_2C_2H_5 \rightarrow CH_3NCS + COS + C_2H_5OH$$

Submitted by Maurice L. Moore and Frank S. Crossley.
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

In a 1-l., round-bottomed, three-necked flask, surrounded by an ice bath and fitted with a mechanical stirrer, a reflux condenser, thermometer, and a 250-cc. dropping funnel, are placed 137 g. (110 cc., 1.8 moles) of carbon disulfide and a cold solution of 72 g. (1.8 moles) of sodium hydroxide in 160 cc. of water. To this mixture, cooled to 10–15°, is added, with stirring, 180 cc. (56 g., 1.8 moles of methylamine) of 35 per cent aqueous methylamine solution (Notes 1 and 2) over a period of thirty minutes. Stirring is continued, and the mixture is warmed gently on a steam bath for one to two hours to ensure complete reaction (Note 3). The bright red solution is cooled to 35–40°, and to it is added over a period of one hour, with stirring, 196 g. (175 cc., 1.8 moles) of ethyl chlorocarbonate (Note 4). The stirring is continued for thirty minutes after all the ethyl chlorocarbonate has been added, at which time the temperature should have fallen to 30–40°. The methyl isothiocyanate, which separates on top, is removed from the reaction mixture and weighs 170–190 g.

The product is dried over 10 g. of sodium sulfate and distilled under atmospheric pressure through a short Vigreux column; the fraction which boils at 115–121° is collected. The yield is 85–100 g. (65–76 per cent of the theoretical amount) (Notes 5 and 6). The product may be further purified by refractionation. The portion which boils at 117–119° is collected.

2. Notes

1. The monomethylamine used in this preparation was a "Commercial Special 35 per cent Solution" obtained from Röhm and Haas Company.

2. Methylamine hydrochloride can be used in place of the commercial aqueous methylamine solution by a slight modification of the above procedure. The carbon disulfide and a solution of 122 g. (1.8 moles) of methylamine hydrochloride in 200 cc. of water are mixed together in the flask, and a cold solution of 144 g. (3.6 moles) of sodium hydroxide in 320 cc. of water is added, with stirring, over a period of thirty minutes. Two equivalents of sodium hydroxide must be used in this case. The remainder of the procedure is the same as with the free base.

3. The temperature gradually rises from 25°, which is that noted at the end of the addition of the methylamine solution, to 75–85°.

4. The temperature may rise rather rapidly during this addition; it is advisable to maintain the rate of addition constant so that the reaction does not become too vigorous.

5. Larger runs, up to 5.4 moles of carbon disulfide, have been made with only a slight reduction in yield.

6. This reaction is general for the preparation of alkyl isothiocyanates in good yields; thus, according to the submitters, ethyl isothiocyanate is obtained in yields of 60–70 per cent from ethylamine hydrochloride.

3. Methods of Preparation

Methyl isothiocyanate has been prepared from methyl thiocyanate by rearrangement with heat [1] and from *N,N'*-dimethylthiuramdisulfide by the action of iodine [2] or by heating with water or alcohol.[3] The most useful method of preparation has been the reaction of methylamine with carbon disulfide to form methyldithiocarbamic acid which is decomposed by steam distillation of the lead salt,[4] or by reaction with ethyl chlorocarbonate.[5]

[1] Hofmann, Ber. **13**, 1349 (1880).
[2] v. Braun, ibid. **35**, 817 (1902).
[3] Freund and Asbrand, Ann. **285**, 166 (1895).

METHYLTHIOUREA

$$CH_3NCS + NH_3 \rightarrow CH_3NHCSNH_2$$

Submitted by Maurice L. Moore and Frank S. Crossley.
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

In a 500-cc. three-necked flask, equipped with a stirrer, a reflux condenser, and a dropping funnel, is placed 140 cc. (34 g.; 2 moles of ammonia) of concentrated ammonium hydroxide solution, and 95 g. (1.3 moles) of methyl isothiocyanate (p. 81), b.p. 115–121°, is added, with stirring, over a period of one hour (Note 1). After the addition has been completed, the condenser is removed and the solution is heated on a water bath for thirty minutes to remove excess ammonia. The solution is then boiled with 2 g. of Norite, filtered, and the filtrate chilled in an ice bath. The methylthiourea crystallizes as a colorless, compact, solid mass, which is collected on a filter, washed three times with 25-cc. portions of ice water, and dried. The first crop of crystals weighs 65–75 g. A second crop amounting to 15–20 g. is obtained by concentrating the mother liquor and washings to a volume of 75 cc. and again chilling in the ice bath. The total yield of methylthiourea, m.p. 119–120.5° (Note 2), is 85–95 g. (74–81 per cent of the theoretical amount) (Notes 3 and 4).

2. Notes

1. The addition of the methyl isothiocyanate should be maintained at a constant rate since the reaction is slow to start; when the mixture has warmed up, the reaction becomes very vigorous and hard to control.

[4] Delépine, Bull. soc. chim. (4) **3**, 641 (1908); Delépine, Compt. rend. **144**, 1125 (1907); Worrall, J. Am. Chem. Soc. **50**, 1456 (1928).
[5] Slotta and Dressler, Ber. **63**, 888 (1930).

2. Further purification by crystallizing from boiling anhydrous alcohol yields a product melting at 120.5–121°.

3. The yield is only slightly higher if purer methyl isothiocyanate is used.

4. This is a general method for the preparation of alkyl thioureas. Ethylthiourea, m.p. 103–106°, has been prepared from ethyl isothiocyanate in the same manner. Di- and tri-alkyl thioureas may be prepared from alkyl isothiocyanates in a similar manner by substituting an equivalent amount of an amine solution in place of the ammonium hydroxide. Thus, *sym.*-dimethylthiourea is prepared from methyl isothiocyanate and methylamine solution. A solution of dimethylamine and methyl isothiocyanate gives trimethylthiourea.

3. Methods of Preparation

Methylthiourea has been prepared from methyl isothiocyanate and ammonia in alcoholic[1] or aqueous[2] solution, from methylammonium thiocyanate,[3] and by heating the methyl or ethyl ester of *N*-methyldithiocarbamic acid with alcoholic ammonia.[4]

[1] Näf, Ann. **265**, 108 (1891).

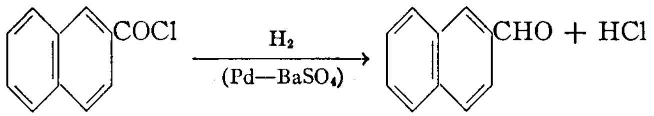
[2] Andreasch, Monatsh. **2**, 276 (1881).

[3] Salkowski, Ber. **26**, 2497 (1893).

[4] Delépine, Compt. rend. **134**, 1222 (1902); Bull. soc. chim. (3) **27**, 812 (1902).

β-NAPHTHALDEHYDE

(2-Naphthaldehyde)



Submitted by E. B. Hershberg and James Cason.
Checked by Nathan L. Drake, Harry D. Anspon, and Ralph Mozingo.

1. Procedure

A 500-cc. three-necked flask, *equipped with ground joints*, is fitted with a mercury-sealed stirrer (Note 1), a reflux condenser,

and a gas-inlet tube extending to a point just above the stirrer. In the flask are placed 57 g. (0.30 mole) of β-naphthoyl chloride (Note 2), 200 cc. of xylene (Note 3), 6 g. of palladium-barium sulfate catalyst,[1] and 0.6 cc. of stock poison solution (Note 4). The top of the condenser is connected by a rubber tube to a 6-mm. glass tube extending to the bottom of a 500-cc. Erlenmeyer flask containing 400 cc. of distilled water and a few drops of phenolphthalein indicator solution. A buret containing approximately 5 *N* sodium hydroxide solution (prepared by dissolving 20.5 g. of analytical reagent sodium hydroxide in water and diluting to 100 cc.) is arranged for delivery into this flask, which for safety should be placed at least 2 ft. away from any flame. Commercial electrolytic hydrogen is passed from a cylinder directly into the reaction flask at such a rate that 100–300 bubbles per minute emerge in the Erlenmeyer flask.

After the air in the reaction flask has been displaced by hydrogen, the flask is heated in an oil bath at 140–150°, the stirrer is started (Note 5), and 1 cc. of alkali is run into the Erlenmeyer flask. The course of the reaction is followed by the rate of hydrogen chloride evolution. The first 5 cc. of alkali should be neutralized in twelve to fifteen minutes, and the reaction should be complete in approximately three hours. About 92 per cent of the theoretical amount of hydrogen chloride (equivalent to 55 cc. of 5 *N* sodium hydroxide solution) is recovered. The end of the reaction is evidenced by a rather abrupt cessation of hydrogen chloride evolution, and the reaction is discontinued at this point.

The flask is cooled, 1–2 g. of Norite added with stirring, and the solution filtered with suction through a hardened filter paper (Note 6). The xylene is removed from the nearly colorless filtrate by flash distillation under diminished pressure. For this purpose, a 125-cc. modified Claisen flask is arranged for vacuum distillation, the usual capillary being replaced by a separatory funnel whose stem extends to the bottom of the flask. The

[1] Prepared by the method described in Houben, "Die Methoden der organischen Chemie," 3rd Ed. Vol. II, p. 500, Verlag Georg Thieme, Leipzig, 1930; Schmidt, Ber. **52**, 409 (1919).

flask is heated in an oil bath at 90–100° and the solution added from the funnel as rapidly as possible without causing accumulation of xylene in the distilling flask. After all the solution has been added, the separatory funnel is replaced by a capillary and the bath temperature raised. After a small fore-run consisting mostly of naphthalene, the β-naphthaldehyde distils at 147-149°/11 mm. (bath temperature 170–180°), leaving a small non-volatile residue. In this way, 34.5–38 g. (74–81 per cent of the theoretical amount) of white aldehyde, m.p. 59–60°, is obtained (Note 7).

2. Notes

1. A tantalum or platinum wire stirrer[2] whose shaft runs in a ball bearing is convenient, but an ordinary all-glass stirrer may be used. The stirrer must be capable of running at a high speed, for the rate of reaction is dependent to a high degree on the speed of stirring. It is also extremely important that the stirrer be carefully lined up so that there is a minimum of splashing of mercury in the seal. If mercury works down into the flask, the reaction will not proceed properly (Note 5).

2. β-Naphthoyl chloride is conveniently prepared from β-naphthoic acid (Org. Syn. **17**, 65) and phosphorus pentachloride. A mixture of 57.4 g. (0.33 mole) of acid and 69 g. (0.33 mole) of phosphorus pentachloride in a 250-cc. modified Claisen distilling flask is warmed on a steam bath in a hood. As soon as the vigorous reaction sets in, the flask is removed from the steam bath until the rapid evolution of hydrogen chloride has moderated, then warmed on the steam bath for one-half hour. After removal of the phosphorus oxychloride at diminished pressure, using a water pump, the acid chloride is distilled. The fraction boiling at 160–162°/11 mm. (bath temperature 170–180°) weighs 57–60 g. (90–95 per cent of the theoretical amount) and melts at 51–52°. The distillation should be carefully conducted, and a quite colorless product should result.

3. One liter of technical xylene is refluxed overnight with 2 g. of sodium, distilled, and stored over sodium.

[2] Hershberg, Ind. Eng. Chem. Anal. Ed. **8**, 313 (1936); Org. Syn. **17**, 31.

4. The quinoline-sulfur poison of Rosenmund and Zetzsche[3] is prepared by refluxing 1 g. of sulfur with 6 g. of quinoline for five hours and diluting the resultant dark brown liquid to 70 cc. with the purified xylene. The literature on the Rosenmund reduction contains many conflicting reports concerning the necessity for a catalyst poison; however, the work of Zetzsche and collaborators[4] indicates that the purity of the solvent is the determining factor. These workers found that by using technical xylene without added poison a good yield of aldehyde could usually be obtained but after the xylene had been purified by distilling over anhydrous aluminum chloride practically no aldehyde was obtained under the same conditions.[5] Instead, products arising from further reduction of the aldehyde were obtained. In view of these results the use of a poison is recommended in order to ensure controlled conditions. The submitters claim that the use of twice the ratio of poison specified has no effect except that of slowing up the reaction; the yield and quality of the product remain the same.

5. The rapid rate of stirring desirable for maximum reaction rate often causes spraying of fine droplets of mercury from the seal. This can be prevented by a layer of paraffin oil over the mercury. It is important for the gas-inlet tube to extend below the surface of the stirred liquid, for absorption of hydrogen occurs chiefly at the rapidly agitated surface.

6. The palladium may be recovered from used catalyst by ignition and solution in aqua regia.[6]

7. According to the submitters, this reaction is quite satisfactory on a small scale and can be used with other acid chlorides. In a 0.05-mole run carried out in the same manner, an 83 per cent yield of β-naphthaldehyde was obtained. 1-Acetoxy-3-naphthaldehyde, m p. 112–114°, was obtained in 70 per cent yield from 0.85 g. of the corresponding acid chloride. Methyl

[3] Rosenmund and Zetzsche, Ber. **54** 436 (1921).

[4] Zetzsche and Arnd, Helv. Chim. Acta **9**, 173 (1926); Zetzsche, Enderlin, Flütsch, and Menzi, ibid. **9**, 177 (1926).

[5] Wahl, Goedkoop, and Heberlein, Bull. soc. chim. (5) **6**, 533 (1939).

[6] Fröschl, Maier, and Heuberger, Monatsh. **59**, 256 (1932).

β-formylpropionate, b.p. 69–70°/14 mm., was also obtained in 65 per cent yield from the acid chloride; reduction proceeds rapidly at 110° in this case.

3. Methods of Preparation

β-Naphthaldehyde has been prepared from β-chloro- or β-bromomethylnaphthalene by use of hexamethylenetetramine,[5] or by oxidation with lead nitrate;[7] from β-naphthoic acid by distillation with calcium formate,[8] or by reduction with sodium amalgam in boric acid solution;[9] from β-naphthylcarbinol by oxidation with chromic acid;[10] and from β-naphthylglyoxylic acid by saponification, heating with aniline, and hydrolysis of the anil.[11] It has been prepared from β-naphthylmagnesium bromide and ethoxymethyleneaniline [12] or orthoformic ester.[13] This reagent has also been converted to the dithioacid with carbon disulfide and this acid converted to β-naphthaldehyde by way of its semicarbazone.[14] β-Naphthaldehyde has been made by the reduction of β-naphthonitrile [15] according to Stephen and by the reduction of β-naphthoyl chloride [16] according to Rosenmund.[17] The procedure described is based on the method developed by Rosenmund [3,17] and applied by him and others to a variety of aldehydes.

[7] Schulze, Ber. **17**, 1530 (1884); Kikkoji, Biochem. Z. **35**, 71 (1911).
[8] Battershall, Ann. **168**, 116 (1873); Ludewig, ibid. **379**, 352 (1911).
[9] Weil, Ber. **44**, 3058 (1911); Weil and Ostermeier, ibid. **54**, 3217 (1921).
[10] Bamberger and Boekmann, ibid. **20**, 1118 (1887).
[11] Rousset, Bull. soc. chim. (3) **17**, 305 (1897).
[12] Monier-Williams, J. Chem. Soc. **1906**, 275; Gattermann, Ann. **393**, 228 (1912).
[13] Tschitschibabin, Ber. **44**, 447 (1911).
[14] Wuyts, Berman, and Lacourt, Bull. soc. chim. Belg. **40**, 665 (1931).
[15] Fulton and Robinson, J. Chem. Soc. **1939**, 200; Williams, J. Am. Chem. Soc. **61**, 2248 (1939).
[16] Rosenmund et al., Ber. **51**, 585, 594 (1918); **54**, 2888 (1921); **55**, 609 (1922).
[17] Fieser and Hershberg, J. Am. Chem. Soc. **62**, 52 (1940).

α-NAPHTHONITRILE

(1-Naphthonitrile)

$$\alpha\text{-}C_{10}H_7Br + CuCN \rightarrow \alpha\text{-}C_{10}H_7CN + CuBr$$

Submitted by M. S. Newman.
Checked by R. L. Shriner and F. J. Wolf.

1. Procedure

In a dry 200-cc. flask fitted with a ground-in reflux condenser and protected from moisture with a calcium chloride tube are placed 66 g. (0.32 mole) of α-bromonaphthalene (Note 1), 35 g. (0.39 mole) of dry powdered cuprous cyanide (Note 2), and 30 cc. of pyridine (Note 3) in the order mentioned. This mixture is heated in a Wood's metal bath (Note 4) at 215–225° for fifteen hours. The resulting dark brown solution is poured while still hot (about 100°) into a flask containing 150 cc. of aqueous ammonia (sp. gr. 0.90) and 150 cc. of water. About 140 cc. of benzene is added, and the flask is stoppered and shaken until all the lumps have disintegrated. After the mixture has cooled to room temperature, 100 cc. of ether is added and the mixture filtered (Note 5). The filtrate is transferred to a 1-l. separatory funnel and the aqueous layer separated (Note 6). The ether-benzene layer is washed successively with (*a*) four 100-cc. portions of dilute aqueous ammonia (Note 7), (*b*) two 100-cc. portions of 6 *N* hydrochloric acid (Note 8), (*c*) two 100-cc. portions of water, and (*d*) two 100-cc. portions of saturated sodium chloride solution. The ether and benzene are removed by distillation from a water bath, and the residue is distilled under reduced pressure from a 125-cc. modified Claisen flask. The temperature rises rapidly, and the yield of colorless α-naphthonitrile, b.p. 173–174°/27 mm. (166–169°/18 mm.) is 40–44 g. (82–90 per cent of the theoretical amount) (Notes 9 and 10).

2. Notes

1. The α-bromonaphthalene (Org. Syn. 10, 14) was redistilled just before use and the fraction boiling at 153–154°/22 mm. taken.

2. "Baker's Analyzed" cuprous cyanide (powdered) was used. The cuprous cyanide must be dry.

3. Pure pyridine dried over barium oxide was used. A considerable amount of heat is liberated on addition of the pyridine to the mixture.

4. A fused salt bath consisting of 8.5 parts (by weight) of sodium nitrite and 10 parts of potassium nitrate has a melting point of about 140° and may replace the metal bath.

5. The cuprammonium solution attacks filter paper and hence this solution is best filtered through a fritted glass filter. Two layers of ordinary toweling cloth on a Büchner funnel may also be used.

6. It is occasionally necessary to add an additional 50 to 100 cc. of ether to facilitate separation.

7. If the final ammoniacal wash solution is not colorless, the ether-benzene solution should be washed with additional 100-cc. portions of dilute aqueous ammonia.

8. If a precipitate separates during this operation it should be removed by filtration.

9. The yields vary with the quality of the cuprous cyanide. One lot of this reagent gave yields of only 60 to 75 per cent. Larger amounts may be run, but the amount of pyridine used should be reduced to decrease the reflux. For a 2-mole run, 160 cc. of pyridine was satisfactory. The yield of the large runs was 81 per cent.

10. α-Chloronaphthalene (b.p. 144–146.5°/29 mm.) may be used in place of α-bromonaphthalene, but twenty-four hours' heating at 245–250° is required. The yields are about the same.

3. Methods of Preparation

α-Naphthonitrile has been prepared from α-naphthylamine by the Sandmeyer reaction,[1] from α-chloronaphthalene,[2] from α-bromonaphthalene[3] by heating with cuprous cyanide, by heating the sodium salt of α-naphthalenesulfonic acid with sodium cyanide,[4] and by heating α-naphthamide with phosphorus pentachloride.[5]

[1] Rupe and Brentano, Helv. Chim. Acta 19, 581 (1936); McRae, J. Am. Chem. Soc. 52, 4550 (1930); Clarke and Read, ibid. 46, 1001 (1924).

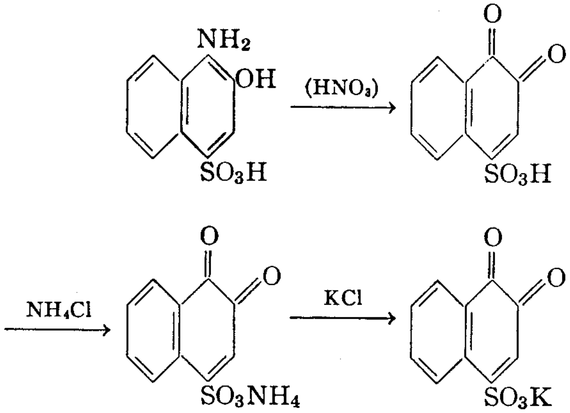
[2] Ger. pat. 293,094 (1916) [Frdl. 13, 269 (1923)].

[3] Newman, J. Am. Chem. Soc. 59, 2472 (1937).

[4] Whitmore and Fox, ibid. 51, 3363 (1929).

[5] Blicke, ibid. 49, 2848 (1927).

1,2-NAPHTHOQUINONE-4-SULFONATE, AMMONIUM AND POTASSIUM



Submitted by E. L. Martin and L. F. Fieser.
Checked by R. L. Shriner and Eldred Welch.

1. Procedure

A mixture of 145 cc. of nitric acid (sp. gr. 1.42) and 400 cc. of water in a 2-l. beaker is cooled to 30° in a slush of ice and water, and 350 g. (1.46 moles) of pure, anhydrous 1-amino-2-naphthol-4-sulfonic acid (Note 1) is weighed into a separate 2-l. beaker. The beaker is removed from the bath; a 10-g. portion of the 1-amino-2-naphthol-4-sulfonic acid is stirred into the solution, and the liquid is then allowed to become entirely motionless. Generally, oxidation starts during this addition; if not, 2 cc. of

concentrated nitric acid is poured carefully down the side of the beaker without stirring. Oxidation commences in one to two minutes and the mixture turns yellow (Note 2).

The beaker is replaced in the ice bath, and 20–25 g. of 1-amino-2-naphthol-4-sulfonic acid is stirred into the mixture by hand. A second portion of 20–25 g. is added immediately and stirred. The mixture begins to froth and is covered with a layer of 100 cc. of ether which serves as an efficient subsident (Note 3). The remainder of the 1-amino-2-naphthol-4-sulfonic acid is added in 20–25 g. portions during the course of three to four minutes, the mixture being stirred well after each addition. Oxides of nitrogen are freely evolved, and a stiff yellow-orange paste is formed. The temperature is maintained between 25° and 30° by vigorous stirring and by controlling the rate of addition of the compound (Note 4). The oxidation is complete within three to four minutes after the last addition and gas is then no longer evolved. The thick mass is stirred until the temperature has dropped to 5–10° and then 175 cc. of saturated ammonium chloride solution (30°) is added.

After the mixture has been cooled to 0°, the ammonium 1,2-naphthoquinone-4-sulfonate is collected on a 20-cm. Büchner funnel and as much of the mother liquor is removed as possible by pressing the cake with a porcelain spatula or glass stopper. The product is washed with three equal portions of a cold mixture of 150 cc. of saturated ammonium chloride solution and 100 cc. of water. The wash solution is removed as completely as possible and the product washed twice with 50-cc. portions of alcohol, followed by 300 cc. of ether in small portions (Note 5). The ammonium 1,2-naphthoquinone-4-sulfonate is spread out in a thin layer and dried to constant weight at 35–40°. An orange, microcrystalline product of bright appearance is thus obtained. The yield is 350–365 g. (94–98 per cent of the theoretical amount). The ammonium salt is of good quality and is sufficiently pure for many purposes. No satisfactory method has been devised for its further purification, but it can be converted into a pure potassium salt as follows.

Seventeen hundred cubic centimeters of water containing

0.3 cc. of liquid bromine is heated in a 2-l. Erlenmeyer flask to 50° on a steam bath (Note 6). The flask is removed, 50 g. of ammonium 1,2-naphthoquinone-4-sulfonate is added, and the mixture is shaken for a few minutes until solution is complete. Three grams of Norite is added, and the solution is stirred for two to three minutes. It is then filtered by suction and the clear orange filtrate transferred to a 4-l. Erlenmeyer flask. Four hundred cubic centimeters of saturated potassium chloride solution (30°) is added rapidly in one portion, and the flask is allowed to stand undisturbed. Orange crystals of potassium salt begin to separate immediately, and after standing for thirty minutes the contents of the flask are cooled to 0° in an ice-salt bath and the potassium 1,2-naphthoquinone-4-sulfonate collected on a 15-cm. Büchner funnel. The solid is washed with 150 cc. of cold, dilute potassium chloride solution (30 cc. of saturated potassium chloride solution added to 120 cc. of water), and then with 150 cc. of alcohol in small portions followed by 300 cc. of ether. The potassium salt is dried to constant weight at 40–50°. The yield is 48–50 g. (90–92 per cent of the theoretical amount based on the ammonium salt used). The product consists of orange needles free of colored decomposition products but still containing traces of ammonium salts. An ammonium-free compound is obtained by a second crystallization. Seventeen hundred cubic centimeters of water containing 0.2 cc. of liquid bromine is heated to 60° in a 2-l. Erlenmeyer flask on a steam bath; the flask is removed, and 50 g. of the potassium salt is added. The salt dissolves rapidly; the solution is filtered with suction; and the clear orange filtrate is transferred to a 4-l. Erlenmeyer flask. Three hundred cubic centimeters of saturated potassium chloride solution is added rapidly in one portion and the flask allowed to stand undisturbed. Orange needles of potassium salt appear in a moment or two, and after standing for thirty minutes, the mixture is cooled to 0° in an ice-salt bath. The crystals are collected, washed, and dried as outlined above. The salt thus obtained weighs 45–49 g. (90–98 per cent of the theoretical amount based on the potassium 1,2-naphthoquinone-4-sulfonate used). This product compared favorably with the

sodium salt prepared by the more elaborate borax process[1] with respect to color, colored decomposition products, and ammonia content (Notes 7 and 8).

2. Notes

1. The 1-amino-2-naphthol-4-sulfonic acid earlier described (Org. Syn. 11, 12) is not quite pure and gives an oxidation product of somewhat inferior quality. The procedure in question yields a gray product containing water of hydration (the percentage yield reported is thus in error). On reinvestigating the matter it has been found that the darkening of the material can be minimized if not prevented entirely, and that the colored impurity can be removed completely by extraction with alcohol. The colorless, anhydrous sulfonic acid required for the present preparation is thus prepared by modifying the earlier procedure in the following respects. By stirring the mixture of nitroso-β-naphthol and sodium bisulfite solution vigorously by hand (wooden paddle), all the soluble product can be dissolved in three to four minutes. The solution is then filtered as rapidly as possible, using two 15-cm. Büchner funnels and changing filter papers frequently. The clear, golden-yellow filtrate is acidified immediately on completion of the filtration. The product is then light gray, whereas, if much time elapses before the bisulfite solution is acidified, the solution turns red and the aminonaphtholsulfonic acid may be deep purple-gray in color. After the product has been collected and washed with water, it is washed with warm alcohol until the filtrate is colorless; 1.5–2 l. of alcohol is required. The product is washed with two 100-cc. portions of ether and dried to constant weight at 60–80° in the absence of light. A pure white, dust-dry product which weighs 370–380 g. (75–78 per cent of the theoretical amount based on the β-naphthol) is thus obtained. This product is used in the present procedure.

If technical 1-amino-2-naphthol-4-sulfonic acid is used, the yield of ammonium 1,2-naphthoquinone-4-sulfonate is 313 g. (84 per cent) of a rust-colored product. If the technical material is washed with 2 l. of warm 95 per cent alcohol the yield is 337 g. (90 per cent) of an orange-colored ammonium salt.

2. It is important that the oxidation start at this point. Should oxidation not begin, a second 1–2 cc. portion of concentrated nitric acid is added; the acid is introduced along the side of the beaker with as little disturbance as possible.

3. It is necessary to add more ether from time to time to replace that which evaporates.

4. The temperature must be kept within this range. At lower temperatures the oxidation is slow and not satisfactory; at higher temperatures the quinone is slightly decomposed.

5. The alcohol and ether remove the small amount of decomposition products and assist in the rapid drying of the product. It is advisable to dry the preparation as rapidly as possible.

6. Aqueous solutions of 1,2-naphthoquinone-4-sulfonate begin to decompose when heated to this temperature in the absence of bromine.

7. Tests for the purity of the product were devised by Folin and later improved by Danielson.[1] A direct comparison of the two preparations revealed no difference in the degree of purity of the product.

8. This purified salt is suitable for use in the procedures of Folin and of Sullivan for the determination of amino acids.

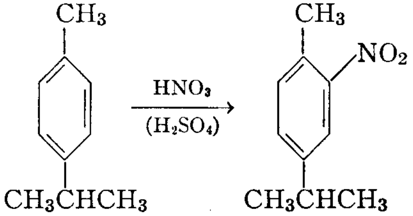
[1] Danielson, J. Biol. Chem. 101, 507 (1933).

3. Methods of Preparation

Salts of 1,2-naphthoquinone-4-sulfonate have been prepared by the oxidation of 2-amino-1-naphthol-4-sulfonic acid with nitric acid,[2] or by the oxidation of the more readily available 1-amino-2-naphthol-4-sulfonic acid with the same reagent.[3,4,5]

[2] Witt and Kaufman, Ber. 24, 3162 (1891).
[3] Folin, J. Biol. Chem. 51, 386 1922).
[4] Böniger, Ber. 27, 24 (1894).
[5] Fieser, J. Am. Chem. Soc. 48, 2929 (1926).

2-NITRO-*p*-CYMENE



Submitted by KENNETH A. KOBE and THOMAS F. DOUMANI.
Checked by C. F. H. ALLEN and JAMES VAN ALLAN.

1. Procedure

A 5-qt. enamel pail or bain-marie jar is fitted with two mechanical stirrers (Note 1) placed off center, a thermometer for reading low temperatures, and a dropping funnel, the lower end of which is placed just over the vortex created by one of the stirrer blades, so that each drop of added liquid is immediately mixed with and diluted by the chilled reaction mixture.

In the pail are placed 1000 g. (544 cc.) of concentrated sulfuric acid and 300 cc. of glacial acetic acid (Note 2), and this mixture is chilled by Dry Ice until the temperature is 0° to −5°. Next, 500 g. (585 cc.) of *p*-cymene (Note 3) is added from the dropping funnel with vigorous stirring, any rise of temperature being prevented by the addition of Dry Ice (Note 4). Concurrently the nitrating mixture is prepared from 369 g. (262 cc.) of nitric acid (sp. gr. 1.42) and 1000 g. (544 cc.) of concentrated sulfuric acid, and cooled to 0–5° by the direct addition of small pieces of Dry Ice (Note 4).

The hydrocarbon emulsion is then cooled to −15° to −10° and the nitrating mixture is admitted dropwise from the dropping funnel over a period of about two hours, avoiding any temperature rise (Notes 4 and 5). Stirring is continued for ten minutes, after which the entire contents of the pail are poured, with adequate stirring, into a mixture of 1 kg. of cracked ice and 1 l. of water. Separation into layers occurs after about two

hours, whereupon the lower acid layer is drawn off by siphoning or by means of a large separatory funnel (Note 6) and extracted twice, using 50-cc. portions of petroleum ether or 500-cc. portions of ether (Note 7). The extracts and crude nitrocymene are combined and washed three times with 300-cc. portions of water (Note 8), and the ether layer is dried by 50 g. of calcium chloride. After the ether is filtered and distilled, the residual liquid is fractionated *in vacuo*, using a 1-l. modified Claisen flask with indented neck. Fractions are collected at 15–17 mm. as follows: up to 125°, 25–30 g. (Note 9); 125–139°, 520–550 g. (78–82 per cent), $n_D^{26°}$ 1.5280; tarry residue, 25–30 g. The product is mainly 2-nitro-*p*-cymene but contains about 8 per cent of *p*-nitrotoluene; it is suitable for reduction [1] to 2-amino-*p*-cymene, from which the *p*-toluidine is readily removed. Upon refractionation of the mixed nitro compounds, the last half is essentially pure 2-nitro-*p*-cymene, b.p. 137–139°/17 mm.; 128–131°/12 mm.; 108°/3 mm., $n_D^{25°}$ 1.5290. The properties of pure 2-nitro-*p*-cymene are as follows: b.p. 126°/10 mm.; 142°/20 mm.; $n_D^{20°}$ 1.5287.

2. Notes

1. It is advisable to use more powerful stirring motors than those usually found in the organic laboratory, since the success of the preparation is so largely dependent on the production of a good emulsion. The checkers employed two "Lightnin" stirrers (Model L mixers) having shafts and blades of Monel metal.

2. On mixing the acids, the temperature rises to about 60°.

3. The authors recommended that a technical grade of cymene be used, since the terpenic impurities present facilitated emulsification. The checkers used both a technical product and one free from terpenes; they encountered no difficulties with emulsification and secured a slightly higher yield (3–4 per cent) with the purified grade. Cymene from different sources varies considerably in its composition.

4. The amounts of Dry Ice given are approximate. The actual quantities depend on the initial temperature and the

rapidity of cooling required. Ordinarily 200 g. is required to cool the nitrating mixture, 500 g. to chill the cymene-sulfuric-acetic acid mixture, and 1500 g. during the actual nitration. The nitrating acid will solidify if chilled too far. It is extremely important to keep the temperatures indicated to secure the best yields, and Dry Ice should be used freely. The carbon dioxide evolved aids in mixing.

5. If the mixture is cooled too much, the emulsion is broken.

6. The separation into layers is not sharp; 10–15 g. of product may be lost with the acid layer at this point (Note 7).

7. The extractions can be omitted with a smaller yield of product. Thus from the first extraction there is obtained approximately 15 g. of nitro compound, and 7 g. from the second.

8. Sometimes an emulsion is formed during washing; this can be broken by the addition of a few cubic centimeters of sulfuric acid and shaking.

9. The fore-run, on refractionation at atmospheric pressure, yields 4–6 g. of impure *p*-cymene, b.p. 160–165°, and 10–13 g. of nitro compound. This latter amount is included in the total yields given in the procedure.

3. Methods of Preparation

2-Nitro-*p*-cymene has always been secured by the nitration of the hydrocarbon, either by the use of mixed sulfuric and nitric acids with [2] or without [3] the addition of acetic acid, or by fuming nitric acid in acetic acid.[4]

[1] Doumani and Kobe, Ind. Eng. Chem. **31**, 264 (1939).

[2] Söderbaum and Widman, Ber. **21**, 2126 (1888); Andrews, J. Ind. Eng. Chem. **10**, 453 (1918); Wheeler and Smithey, J. Am. Chem. Soc. **43**, 2613 (1921); Phillips, ibid. **44**, 1777 (1922); Demonbreum and Kremers, J. Am. Pharm. Assoc. **12**, 296 (1926) [C. A. **17**, 3906 (1923)]; Kobe and Doumani, Ind. Eng. Chem. **31**, 257 (1939).

[3] Andrews, U. S. pat. 1,314,920 [C. A. **13**, 2765 (1919)]; Selden, Brit. pat. 142,226 [C. A. **14**, 2645 (1920)].

[4] Schumow, J. Russ. Phys. Chem. Soc. (1) **19**, 119 (1887); Ber. Ref. **20**, 218 (1887).

dl-PHENYLALANINE

(*dl*-α-Amino-β-phenylpropionic Acid)

$$CH_2(CO_2C_2H_5)_2 + C_6H_5CH_2Cl \xrightarrow{(NaOC_2H_5)} C_6H_5CH_2CH(CO_2C_2H_5)_2$$

$$C_6H_5CH_2CH(CO_2C_2H_5)_2 \xrightarrow[\text{(then HCl)}]{(KOH)} C_6H_5CH_2CH(CO_2H)_2$$

$$C_6H_5CH_2CH(CO_2H)_2 + Br_2 \rightarrow C_6H_5CH_2CBr(CO_2H)_2 + HBr$$

$$C_6H_5CH_2CBr(CO_2H)_2 \xrightarrow{\text{heat}} C_6H_5CH_2CHBrCO_2H + CO_2$$

$$C_6H_5CH_2CHBrCO_2H + 2NH_3 \rightarrow C_6H_5CH_2CHNH_2CO_2H + NH_4Br$$

Submitted by C. S. Marvel.*
Checked by Lee Irvin Smith, R. T. Arnold, and K. L. Howard.

1. Procedure

(*A*) *Diethyl Benzylmalonate.*—To 2500 cc. of absolute ethanol in a 5-l. three-necked flask set on a steam cone and equipped with a mercury-sealed stirrer, reflux condenser, and a 500-cc. dropping funnel is added 115 g. (5 gram atoms) of sodium cut in small slices. When all the sodium has reacted, a calcium chloride tube is placed on the condenser and 830 g. (5.18 moles) of diethyl malonate is added through the separatory funnel in a steady stream. This is followed by the dropwise addition of 632 g. (5 moles) of benzyl chloride over a period of two to three hours. The mixture is refluxed, with stirring, until neutral to moist litmus paper (about eight to eleven hours). The reflux condenser is then exchanged for a downward condenser, and the alcohol is distilled into another 5-l. three-necked flask equipped with a reflux condenser (Note 1). About three hours is required to remove the alcohol, and slightly more than 2 l. is recovered.

*These directions are the result of the efforts of dozens of men who have worked on the preparation of phenylalanine at the University of Illinois during the past twenty years.

The residue is then treated with no more than 2 l. of water (Note 2) and shaken; if necessary, salt is added to make the ester layer separate sharply from the aqueous layer. The combined ester layers from two such runs are distilled from a 5-l. two-necked flask fitted with a well-wrapped 18-mm. Vigreux column. The fraction distilling at 145–155°/5 mm. is collected; it amounts to 1265–1420 g. (51–57 per cent of the theoretical amount). The residue is chiefly diethyl dibenzylmalonate.

(*B*) *α-Bromo-β-phenylpropionic Acid.*—Eight hundred and sixty grams of technical potassium hydroxide is dissolved in 850 cc. of water in a 12-l. round-bottomed flask equipped with a stirrer and set on a large steam cone. While the solution is still hot, 1000 g. (4 moles) of diethyl benzylmalonate is added from a dropping funnel over a period of one hour. The removal of alcohol vapors is facilitated by placing a tube connected to the water pump in the mouth of the flask. Heating and stirring are continued for three hours, and more water is added, if necessary, to keep the mass from solidifying. The flask is then cooled and the contents poured into a crock surrounded by an ice bath and equipped with a stirrer. Five hundred grams of ice is added to lower the temperature and, when it reaches 20°, technical hydrochloric acid is added at such a rate that the temperature does not rise. The addition is slow at first, but more rapid when the excess alkali has been neutralized. The solid monopotassium salt which separates is returned to solution by adding the acid more rapidly and stirring by hand. When the reaction mixture is acid to Congo red paper, an excess of 150 cc. of acid is added and the contents of the crock are transferred to a 12-l. round-bottomed flask fitted with a stopper containing a large stopcock which barely pierces the stopper, and a glass tube which reaches to the bottom of the flask. In this way the flask may be used as a large separatory funnel if the stopper is wired in tightly.

The benzylmalonic acid is extracted with four 1-l. portions of ether; the ether extracts are combined in a 5-l. flask and allowed to stand over 150 g. of calcium chloride overnight. The ether layer is then decanted into a 5-l. flask equipped with an efficient reflux condenser, mercury-sealed stirrer, and dropping funnel. Two hundred and twenty-five cubic centimeters of dry bromine is dropped in at such a rate that the ether refluxes (Note 3). The time required is about four hours. After the complete addition of bromine, 1 l. of water is added through the dropping funnel at such a rate that the ether merely refluxes (Note 4).

The ether layer of bromobenzylmalonic acid is separated by decantation and the ether removed by distillation. The residue is then decarboxylated by heating to a temperature of 130–135° in a 3-l. flask in an oil bath for five hours.

(*C*) *dl-Phenylalanine.*—The crude bromo acid is divided into four portions and each portion is added to 2 l. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask. The flask is well shaken, a rubber stopper is wired in, and the mixture is allowed to stand for a week. The contents of the four amination flasks (Note 5) are then combined in a 12-l. flask, 20 g. of Norite is added, and the flasks are heated on a steam cone overnight. The ammonia which is evolved is conducted into a gas-absorption trap or merely led into water by a tube from the flask. The solution is filtered while still hot; on cooling most of the phenylalanine precipitates. This is filtered, washed with 250 cc. of methanol, and the filtrate evaporated under the pressure of a water pump until more crystals form. The solution is then cooled and an additional crop of phenylalanine obtained, which is also washed with methanol. The yield of crude product is 500 g., but it is slightly wet; if it is dried overnight in an oven at about 80°, it will weigh 460 g. This need not be done, however, as the yield of pure product is the same whether or not the crude product is dried.

The phenylalanine is recrystallized as follows: the crude product is dissolved in 9 l. of water heated to 95° on a steam cone, treated with 15 g. of Norite, and filtered. Three liters of alcohol is added and the solution cooled in the icechest overnight. The yield of pure product amounts to 367 g. An additional 45 g. may be obtained by evaporating the mother liquor under reduced pressure until crystals separate, adding an amount of alcohol equivalent to one-third the volume of the concentrated mother

liquor, and cooling. Additional material may be obtained by continuing to work down all mother liquors. The yield, 412 g., is 62.4 per cent of the theoretical amount based on the diethyl benzylmalonate. The white crystals decompose at 271–273° (uncorr.) in a closed capillary (Note 6).

2. Notes

1. The sodium required for the next run can be added to the second flask as the alcohol distils into it.

2. Usually 1.5 l. of water suffices, and it is not necessary to add salt.

3. To start the bromination 10 cc. of bromine is added and the solution stirred until decolorized. After the reaction has been started in this manner, it runs very smoothly. When large amounts of the amino acid are to be prepared, it is more convenient to double the portion used in the bromination step.

4. Care must be taken not to add the water too fast, as the reaction mixture will foam out of the flask.

5. The aminations are usually colored, and frequently the flasks contain small deposits of oil on the bottom. This oil disappears in subsequent treatment.

6. The product thus obtained has the calculated amino nitrogen content.

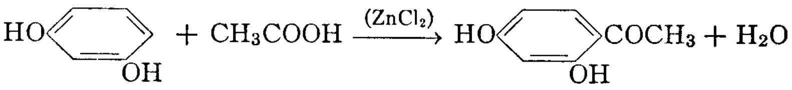
3. Methods of Preparation

Methods of making *dl*-phenylalanine have been summarized (Org. Syn. **14**, 82). The method described here is essentially the one originally described by Fischer.[1] For the preparation of large amounts of amino acids it is undoubtedly the cheapest and best procedure.

[1] Fischer, Ber. **37**, 3064 (1904).

RESACETOPHENONE

(Acetophenone, 2,4-dihydroxy-)



Submitted by S. R. Cooper.
Checked by Nathan L. Drake, Harry D. Anspon, and Ralph Mozingo.

1. Procedure

One hundred and sixty-five grams (1.2 moles) of anhydrous zinc chloride (Note 1) is dissolved with the aid of heat in 165 g. (158 cc., 2.7 moles) of glacial acetic acid, which has been placed in a 1-l. beaker. To this hot mixture (about 140°), 110 g. (1 mole) of resorcinol is added with constant stirring. The solution is heated on a sand bath until it *just* begins to boil (about 152°). The flame is then removed and the reaction allowed to complete itself at a temperature not in excess of 159° (Note 2). After standing on the sand bath without further heating for twenty minutes, the solution is diluted with a mixture of 250 cc. of concentrated hydrochloric acid and 250 cc. of water. The dark red solution is placed in an ice bath and cooled at 5°. The resulting precipitate is collected on a filter and washed free from zinc salts with 1 l. of dilute (1 : 3) hydrochloric acid in 200-cc. portions. This orange-red product, after drying, weighs 104–110 g. and melts at 141–143°. It is distilled under reduced pressure (Note 3), and boils at 180–181° at 10 mm. (147–152° at 3–4 mm.). After most of the product has distilled, the temperature rises sharply, and the operation is discontinued when the temperature reaches 190°. The light yellow distillate is removed from the receiver with hot ethyl alcohol and the alcohol evaporated (Note 4). This product weighs 100–106 g. It is further purified as follows: the substance is dissolved in 1800 cc. of hot dilute (1 : 11) hydrochloric acid, filtered hot, and cooled to 5°. The crystals are removed by filtration, washed with two

200-cc. portions of ice water, and dried. The yield of tan-colored resacetophenone, melting at 142–144°, is 93–99 g. (61–65 per cent of the theoretical amount).

2. Notes

1. Although finely ground zinc chloride dissolves more rapidly, lumps or sticks are satisfactory.

2. If the temperature rises much above the initial boiling point, the yield of red product increases at the expense of resacetophenone formation. The boiling point also may vary slightly.

3. Any convenient apparatus for distillation of a solid may be used.

4. It is convenient to remove most of the material by melting and pouring it out of the receiver. The remainder is removed with hot alcohol.

3. Methods of Preparation

Resacetophenone has been prepared by heating resorcinol with zinc chloride and acetic acid,[1,2] with zinc chloride and acetic anhydride,[2] and with zinc chloride and acetyl chloride.[3] It has also been prepared by the action of zinc chloride on resorcinol diacetate,[2] by heating 4-methylumbelliferone with potassium hydroxide,[4] by heating resacetophenone carbonic acid,[5] and by the action of acetyl chloride on resorcinol.[6]

[1] Robinson and Shah, J. Chem. Soc. **1934**, 1491.
[2] Nencki and Sieber, J. prakt. Chem. (2) **23**, 147 (1881).
[3] Eijkman, Chem. Weekblad I, 453 (1904) [Chem. Zentr. **75**, II, 1597 (1904)].
[4] Pechmann and Duisberg, Ber. **16**, 2119 (1883).
[5] Liebermann and Lindenbaum, ibid. **40**, 3570 (1907).
[6] Cox, Rec. trav. chim. **50**, 848 (1931).

TETRANITROMETHANE

$$4(CH_3CO)_2O + 4HNO_3 \rightarrow C(NO_2)_4 + 7CH_3CO_2H + CO_2$$

Submitted by Poe Liang.
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

In a 250-cc. Erlenmeyer flask provided with a two-holed stopper which has a slit cut in one edge to serve as an air vent and which holds a thermometer, the bulb of which reaches almost to the bottom of the flask, is placed 31.5 g. (0.5 mole) of anhydrous nitric acid (Note 1). The flask is cooled below 10° in ice-water, and 51 g. (0.5 mole) of acetic anhydride (Note 2) is slowly added from a buret through the second hole in the stopper in portions of about 0.5 cc. at a time. The temperature of the reaction mixture is never allowed to rise above 10° (Note 3). After about 5 cc. of the acetic anhydride has been added the reaction becomes less violent, and larger portions, increasing gradually from 1 to 5 cc., may be introduced at a time with constant shaking. After all the acetic anhydride has been added, the stopper and the thermometer are removed. The neck of the flask is wiped clean with a towel, and the flask is then covered with an inverted beaker and allowed to come up to room temperature in the original ice bath (Note 4).

The mixture is allowed to stand at room temperature for seven days (Note 5), and the tetranitromethane is separated by pouring the mixture into 300 cc. of water in a 500-cc. round-bottomed flask and steam distilling (Note 6). The tetranitromethane passes over with the first 20 cc. of the distillate. The heavy product is separated from the upper layer of water, washed first with dilute alkali, finally with water, and dried over anhydrous sodium sulfate. The yield of tetranitromethane is 14–16 g. (57–65 per cent of the theoretical amount). *The product should not be distilled, as it may decompose with explosive violence.* Tetranitromethane must be kept out of contact with aromatic

compounds except in *very small* test portions, since violently explosive reactions can occur (Note 7).

2. Notes

1. The anhydrous nitric acid (sp. gr. > 1.53) is most easily obtained by slowly distilling ordinary fuming nitric acid from its own bulk of concentrated sulfuric acid. If ordinary concentrated nitric acid (sp. gr. 1.42) is used, it is advisable to distil twice from equal volumes of sulfuric acid. A technical grade of fuming nitric acid having a specific gravity of 1.60 was found to give satisfactory yields when used without further treatment; but an equivalent amount of a weaker commercial acid, corresponding to 98 per cent nitric acid by gravity, gave considerably lower yields. The use of more than the calculated amount of nitric acid decreases the yield of tetranitromethane.

2. According to the submitter, the purity of acetic anhydride is not so important as that of the nitric acid. Equivalent amounts of 99–100 per cent and 94–95 per cent acetic anhydride gave practically the same yield of tetranitromethane.

3. If the flask is not cooled, the reaction proceeds more and more vigorously as the temperature rises and may, if unchecked, become violent.

4. If the flask is removed from the ice bath after the addition of the anhydride, and allowed to stand at room temperature, the reaction may become violent with great loss of product.

5. The yield is only 35 per cent after two days and no greater than 65 per cent after ten or fifteen days. If it should be necessary to obtain the product in shorter time, the reaction mixture may be allowed to stand at room temperature for forty-eight hours and then slowly heated to 70° during an interval of three hours and maintained at 70° for one hour longer before pouring into water. The yield of a run carried out in this way was, according to the submitter, 40 per cent.

6. It is most convenient to use a 50-cc. graduated separatory funnel as the receiver during the steam distillation, if it is desired to estimate roughly the yield of tetranitromethane, the density of which is 1.65 at 15°.

7. Tetranitromethane is a valuable reagent for detecting the presence of double bonds, especially those which do not give the ordinary reactions of such linkages.[1]

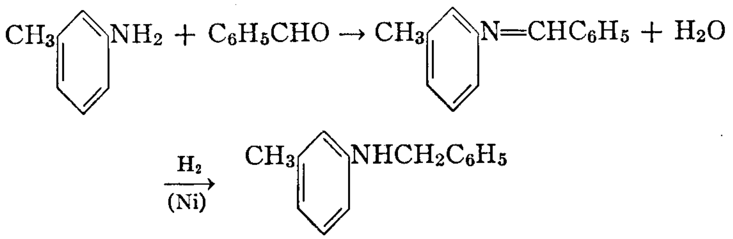
3. Methods of Preparation

The procedure described is essentially that of Chattaway.[2] Tetranitromethane has also been prepared by nitrating nitroform,[3] from acetic anhydride by the action of diacetylorthonitric acid,[4] from iodopicrin and silver nitrite,[5] from acetyl nitrate by heating with acetic anhydride or glacial acetic acid,[6] from nitrobenzene by distilling with a mixture of nitric acid and fuming sulfuric acid,[7] by adding acetic anhydride to nitrogen pentoxide or a mixture of nitrogen pentoxide and nitrogen peroxide,[8] by the action of acetic anhydride on highly concentrated nitric acid,[9] from toluene by nitration,[10] from acetylene by the action of nitric acid,[11] from nitrobenzene and a mixture of nitric and fuming nitric acids,[12] and from acetylene and ethylene by the action of nitric acid in the presence of a catalyst.[13]

[1] Meyer, H., "Analyse und Konstitutionsermittlung organischer Verbindungen," 6th Ed., p. 773, Julius Springer, Vienna, 1938; Ruzicka, Huyser, Pfeiffer, and Seidel, Ann. **471**, 21 (1929).
[2] Chattaway, J. Chem. Soc. **1910**, 2099; Chem. News **102**, 307 (1910).
[3] Schischkoff, Ann. **119**, 247 (1861).
[4] Pictet and Genequand, Ber. **36**, 2225 (1903).
[5] Hantzsch, ibid. **39**, 2478 (1906).
[6] Pictet and Khotinsky, Compt. rend. **144**, 210 (1907); Ber. **40**, 1163 (1907).
[7] Claessen, Ger. pat. 184,229 [C. A. **1**, 2524 (1907)].
[8] Schenck, Ger. pats. 211,198, 211,199 [C. A. **3**, 2205 (1909)].
[9] Bayer and Co., Brit. pat. 24,299 [C. A. **5**, 2305 (1911)] and Ger. pat. 224,057; Berger, Compt. rend. **151**, 813 (1910) and Bull. soc. chim. (4) **9**, 26 (1911).
[10] Will, Ber. **47**, 704 (1914).
[11] Orton, Brit. pat. 125,000; Orton and McKie, J. Chem. Soc. **1920**, 283.
[12] McKie, J. Soc. Chem. Ind. **44**, 430T (1925).
[13] McKie, J. Chem. Soc. **1927**, 962.

m-TOLYLBENZYLAMINE

(*m*-Toluidine, *N*-Benzyl)



Submitted by C. F. H. Allen and James Van Allan.
Checked by Nathan L. Drake and Ralph Mozingo.

1. Procedure

One hundred and six grams (1 mole) of benzaldehyde (Note 1) and 107 g. (1 mole) of *m*-toluidine are mixed in a suitable flask; the temperature rises to about 60° (Notes 2 and 3). The mixture is cooled below 35° in cold water, 200 cc. of ether is added, and the solution is placed in the steel reaction vessel of a high-pressure hydrogenation apparatus.[1,2] Eight to ten grams of Raney nickel catalyst (p. 15) is added, the bomb is closed, and hydrogen is admitted up to 1000 lb. pressure (Note 4). The bomb is shaken continuously at room temperature for fifteen minutes (Note 5). The contents are removed, and the bomb is washed out with two 200-cc. portions of ether. After the catalyst has been separated by filtration (Note 6), the ether is removed by distillation and the product is distilled from a modified Claisen flask (Note 7). After a small fore-run the *N*-benzyl-*m*-toluidine boils at 153–157°/4 mm.; 315–317°/760 mm. The yield is 175–185 g. (89–94 per cent of the theoretical amount) (Notes 8 and 9).

[1] American Instrument Company, Silver Spring, Maryland.
[2] Parr Instrument Company, Moline, Illinois.

2. Notes

1. Technical grades of benzaldehyde (b.p. 57–59°/8 mm.) and *m*-toluidine (b.p. 76–77°/7 mm.) are satisfactory.
2. It is unnecessary to isolate the Schiff base.
3. The ether used as solvent may be replaced by an equal amount of 95 per cent alcohol. If alcohol is used, cooling is unnecessary.
4. The initial pressure of hydrogen used is determined by the apparatus available. The drop in pressure depends upon the size of the bomb.
5. With a less active Raney nickel catalyst it may be necessary to carry out the reduction at a somewhat higher temperature. If necessary, the reaction mixture may be heated slowly to 60° and the reduction carried out at this temperature. The yield is then somewhat lower (82–84 per cent).
6. The catalyst is filtered through paper on a Büchner funnel. Owing to its activity, suction should be discontinued as soon as all the liquid has passed through. If this precaution is not observed, a fire may result.
7. In some instances (*o*-tolylbenzylamine), a part of the product may crystallize and can be filtered.
8. The hydrochloride, m.p. 198–199°, may serve for characterization.
9. According to the submitters, other aromatic aldehydes and amines may be used in a similar manner with essentially the same yield of product. The exact procedure for isolation of the amine will depend upon its physical properties. Benzaldehyde and *o*-toluidine yield *o*-tolylbenzylamine, m.p. 56–57° (hydrochloride, m.p. 165–166°), while *p*-tolylbenzylamine, obtained from *p*-toluidine, has a b.p. 162–163°/5 mm. (hydrochloride, m.p. 181–182°).

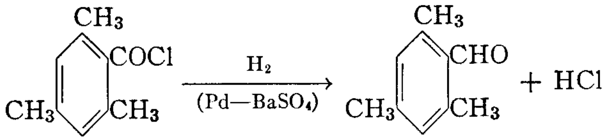
3. Methods of Preparation

N-Benzyl-*m*-toluidine has been prepared by the electrolytic reduction of benzal-*m*-toluidine.[3]

[3] Law, J. Chem. Soc. 1912, 154.

2,4,6-TRIMETHYLBENZALDEHYDE

(β-Isodurylaldehyde)



Submitted by R. P. Barnes.
Checked by Nathan L. Drake, Harry D. Anspon, and Ralph Mozingo.

1. Procedure

A 1-l. three-necked flask *with ground-glass joints* is fitted with a mercury-sealed stirrer (Notes 1 and 2), a glass tube of 6-mm. internal diameter which runs to the bottom of the flask, and a Friedrich condenser, protected by a drying tube. A solution of 90 g. (0.49 mole) of mesitoyl chloride (p. 77) in 270 g. of carefully dried xylene is placed in the flask together with 20 g. of palladium-barium sulfate (Note 3). The contents of the flask are refluxed gently while a stream of hydrogen (Note 4), which has been freed from oxygen by passage through Fieser's solution,[1] and dried by passage through concentrated sulfuric acid followed by a drying tube of Drierite (Note 5), is bubbled through the suspension until hydrogen chloride ceases to be evolved (Note 2). The catalyst is then removed by filtration and the xylene distilled. The residual liquid is transferred to a 125-cc. modified Claisen flask and distilled. The product boils at 96–98°/6 mm., and weighs 53–60 g. (70–80 per cent of the theoretical amount) (Note 6).

2. Notes

1. The stirrer is not essential, but without it the time required for the reduction is increased about threefold.

2. The course of the reaction may be followed conveniently by passing the exit gases into water and titrating with approximately 1 *N* sodium hydroxide. The time for complete reduction is about six to seven hours with stirring, and about eighteen hours with no stirrer.

3. The palladium-barium sulfate is prepared by the method described by Houben.[2] The barium sulfate should be freshly precipitated material.

4. The checkers found that electrolytic hydrogen directly from the cylinder without purification gives only a slightly decreased yield.

5. Dehydrite or Anhydrone should not be used because of the danger of sulfuric acid spraying into it. Drierite is much more efficient than calcium chloride.

6. This preparation illustrates Rosenmund's method of synthesizing aldehydes without use of a poisoned catalyst. See p. 84 for the more general form of the method.

[1] Fieser, J. Am. Chem. Soc. **46**, 2639 (1924).

3. Methods of Preparation

2,4,6-Trimethylbenzaldehyde has been prepared from mesitylglyoxylic acid,[3,4] from mesitylene, nickel carbonyl, and aluminum chloride,[5] and in excellent yield from mesitylene, hydrogen cyanide, and hydrogen chloride, as well as from mesitylene, carbon dioxide, and hydrogen chloride, in the presence of aluminum and cuprous chlorides.[6] The above method is that applied to the preparation of other aldehydes by Rosenmund and Zetzsche.[7]

[2] Houben, "Die Methoden der organischen Chemie," 3rd Ed., Vol. II, p. 500, Verlag Georg Thieme, Leipzig, 1930; Schmidt, Ber. **52**, 409 (1919).

[3] Bouveault, Compt. rend. **124**, 157 (1897).

[4] Feith, Ber. **24**, 3542 (1891).

[5] Dewar and Jones, J. Chem. Soc. **1904**, 219.

[6] Bayer and Co., Ger. pat. 98,706 [Chem. Zentr. **69**, II, 952 (1898)]; Ger. pat. 99,568 [Chem. Zentr. **70**, I, 461 (1899)].

[7] Rosenmund, Ber. **51**, 585 (1918); Rosenmund and Zetzsche, ibid. **54**, 425 (1921).

SUBJECT INDEX

(This Index comprises material from Volumes 20 and 21 of this series; for Volumes I through IX see Collective Volume I, for Volumes X through XIX see Volume XIX.)

Names in small capital letters refer to titles of individual preparations. A number in ordinary bold-face type denotes volume. A number in bold-face italics refers to preparative directions for substances formed either as principal products or as by-products; a number in ordinary type indicates a page on which the compound or subiect is mentioned in connection with other preparations. For example, ACETONE CYANOHYDRIN, **20**, 42, ***43***, indicates that acetone cyanohydrin is mentioned on page 42 and that directions for its preparation are given in detail on page 43 of Volume 20.

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